FORMULATION DEVELOPMENT AND EVALUATION OF VALSARTAN SODIUM SUSTAINED RELEASE TABLETS

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CERTIFICATE

This is to certify that this dissertation entitled

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For the partial fulfillment of the requirements for the award of Degree of Master of Pharmacy in Pharmaceutics, carried out in Department of Pharmaceutics, Padmavathi College of Pharmacy and Research Institute, under my guidance and supervision.

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LIST OF GRAPHS

LIST OF ABBREVIATIONS

MSC	Maximum Safe Concentration
MEC	Minimum Effective Concentration
GIT	Gastro Intestinal Tract
TI	Therapeutic Index
EOP	Elementary Osmotic Pump
TPR	Total Peripheral Resistance
ACE	Angiotensin Converting Enzyme
BVD	Blood Vessel Dilator
TD	Tapped Density
MCC	Micro Crystalline Cellulose
SRDDS	Sustained Release Drug Delivery Systems
BD	Bulk Density
XRD	X Ray Diffraction
HPMC	Hydroxy Propyl Methyl Cellulose
PVP	Poly Vinyl Pyrrolidine
EC	Ethyl Cellulose
FDT	Fast Dissolving Tablet
SEM	Scanning Electron Microscopy
CI	Carr's Index
ICH	International Conference of Harmonisation

1. INTRODUCTION

1.1 An Overview of Sustained Release Dosage Forms

Sustained release tablets and capsules are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect. Typically, sustained release products provide an immediate release of drug that promptly produces the desired therapeutic effect, followed by gradual release of additional amounts of drug to maintain this effect over a predetermined period. The sustained plasma drug levels provide by sustained release products often times eliminates the need for night dosing, which benefits not only the patients but the care given as well.[1]

The basic rationale of a sustained drug delivery system is to optimize the Biopharmaceutical, Pharmacokinetic and Pharmaco dynamic properties of a drug in such a way that its utility is maximized through reduction in side effects and cure or control of condition in the shortest possible time by using smallest quantity of drug, administered by the most suitable route.

The novel system of drug delivery offer a means of improving the therapeutic effectiveness of incorporated drugs by providing sustained, controlled delivery and / or targeting the drug to desired site. The goal of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. There is a continuously growing interest in the pharmaceutical industry for sustained release oral drug delivery systems. There is also a high interest for design a dosage formulation that allows high drug loading, particularly for actives with high water solubility. Oral route has been the most popular and successfully used for sustained delivery of drugs because of convenience and ease of administration, greater flexibility in dosage form design and ease of production and low cost of such a system.

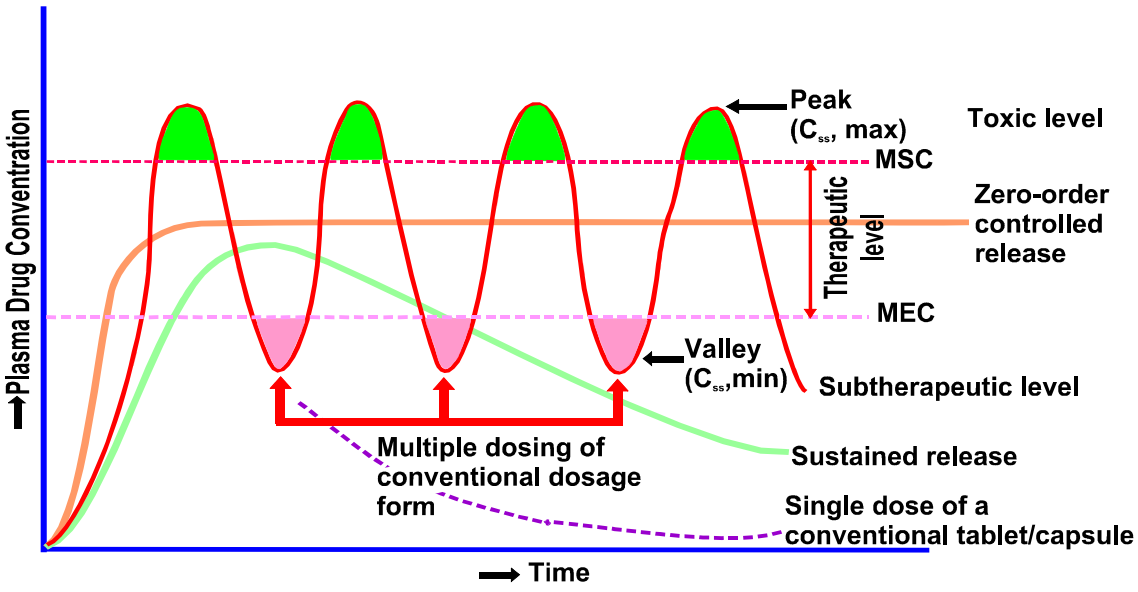
The sustained release systems for oral use are mostly solid and based on dissolution, diffusion or a combination of both mechanisms in the control of release of

drugs. In this type of dosage forms, a sufficient amount of drug is initially made available to the body to cause a desired pharmacological response.

When a conventional dosage form is administered, the concentration of drug in the blood stream will attain a "therapeutic range" necessary for the action of the drug. This therapeutic range would be maintained for some time and finally the concentration drops below this range rendering the drug therapeutically inactive. An ideal drug delivery system involves two prerequisites. It should deliver the drug at a rate desired by the needs of the body and over the period of treatment.

This necessitates steady state blood levels or tissue levels that are therapeutically effective and nontoxic for an extended period of time. It should channel the active entity to the site of action. Advanced research in pharmaceutical technology would find several controlled release dosage forms in the market. These products have been identified by various names as "sustained release", "prolonged release", "controlled release", "timed release", and "delayed release".

Fig No: 1 An hypothetical plasma concentration-time profile from conventional, multiple dosing and single doses of sustained and controlled delivery formulations [2]



1.2 Selection Criteria of Drug for SR Formulation

Half-life should be 2-8 hours.

It should not undergo extensive first –pass metabolism.

It should be stable in GIT.

Compounds with high partition coefficient are better to choose.

Lower limit of solubility of a drug is 0.1 mg/ml.

Drugs absorbed throughout GIT are better candidates.

Table.No:1 Characteristics of Drugs Unsuitable for oral Sustained Release Forms

Characteristics	Drugs
Not effectively absorbed in the lower intestine	Riboflavin, Ferrous salts
Absorbed and excreted rapidly short biologic half-lives (<1hr)	Penicillin G, Furosemide
Long biological half-lives (>12hr)	Diazepam, Phenytoin
Large doses required (>1g)	Sulphonamides
Cumulative action and undesirable side effects, Drugs with low therapeutic indices	Phenobarbital, Digitoxin
Precise dosage titrated to individual is require	Anticoagulants,cardiac glycosides
No clear advantage for sustained release formulation	Griseofulvin.

1.3 Terminology

In the past, many of the terms used to refer to therapeutic systems of controlled and sustained release have been used in an inconsistent and confusing manner. Although descriptive terms such as "timed release" and "prolonged release" give excellent manufacturer identification, they can be confusing to health care professionals. Several descriptions have been given to sustained and controlled release[3]. Defined **sustained release** as "Any dosage form that provide medication over an extended time" and **controlled release** as "Any dosage form which is able to provide some actual therapeutic control, whether this can be of temporal nature, spatial nature, or both". In other words, controlled release system attempts to control drug concentrations in the target tissue. This correctly suggests that there are sustained release systems that cannot be considered controlled release systems. The terminologies, which are frequently used in practice, are given below:

- **Zero-order release**
- **Sustained release**
- **Controlled release**
- **Prolonged release**
- **Repeat action tablets**
- **Delayed-release systems**

In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually achieved by attempting to obtain **zero-order release** from the dosage form. Zero-order release constitutes drug release from the dosage that is independent of the amount of drug in the delivery system. Sustained release systems generally do not attain this type of release and usually try to obtain zero-order release by providing drug in a slow first order fashion. Systems that are designated as prolonged release can also be considered as attempts at achieving sustained release delivery. Repeat action tablets are an alternative method of sustained release in which multiple doses of a drug are contained with in a dosage form, and each dose is released at periodic interval. Delayed release systems, in contrast, may

not be sustaining, since often the function of these dosage form is to maintain the drug within the dosage form for some time before release. Commonly, the release rate of drug is not altered and does not result in sustained delivery once drug release has begin. Enteric coating tablets are an example of this type of dosage form[4] **.**

Controlled release, although resulting in a zero order delivery system, may also incorporate methods to promote localization of the drug at an active site. In some cases, a controlled release system will not be sustaining, but will be concerned strictly with localization of the drug. Site specific systems and targeted delivery systems are the descriptive terms used to denote this type of delivery control**.**

The goal of controlled release systems is to achieve a delivery profile that would yield a high blood level of the drug over a long period of time. With traditional tablets, the drug level in the blood follows the profile shown in figure 1 in which level rises after each administration of the drug and then decreases until the next administration. The key point with traditional drug administration is that the blood level of the agent should remain between a maximum value, which may represent toxic level, and a minimum value, below which the drug is no longer effective. In controlled drug delivery systems designed for long term administration the drug level in the blood follow the profile shown in figure 1 remaining constant, between the desired maximum and minimum, for an extended period of time**.**

Several types of modified-release drug products are recognized [4].

- **Extended release drug products**: A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release, and long-acting drug products.
- **Delayed release drug products**: A dosage form that releases a discrete portion or portions of drug at a time or at times other than promptly after administration, although one portion may be released promptly after administration. Enteric-coated dosage forms are the most common delayed-release products.

- **Targeted release drug products**. A dosage form that releases drug at or near the intended physiologic site of action. Targeted-release dosage forms may have either immediate or extended release characteristics.
- **Controlled release drug product*:*** was previously used to describe various types of oral extended release-rate dosage forms, including sustained release, sustainedaction, prolonged action, long action, slow release, and programmed drug delivery.

1.4 Advantages of sustained release formulations [4, 5]

Sustained release formulations have many advantages over traditional, immediate release products.

- Improved patient convenience and compliance due to less frequent drug administration.
- Reduction in fluctuation in steady state levels and therefore better control of disease condition and reduced intensity of local or systemic side effects.
- Increased safety margin of high potency drugs due to better control of plasma levels.
- Maximum utilization of drug enabling reduction in total amount of dose administered.
- Reduction in health care costs through improved therapy, shorter treatment period, less frequency of dosing and reduction in personnel time to dispense, administer and monitor patients **.**

1.5. Disadvantages of sustained release formulations

- Decreased systemic availability in comparison to immediate release conventional dosage forms; this may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH depent solubility, etc.
- Poor *in vitro-in vivo* correlation.

- Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
- Higher cost of formulation**.**

1.6. Factors influencing the design and performance of sustained release products

The type of delivery system and route of administration of the drug presented in sustained drug delivery system may depend upon two properties. They are:

a) Physicochemical properties of drugs
b) Biological factors.

a) Physicochemical Properties

1. Dose size

For orally administered systems, there is an upper limit to the bulk size of the dose to be administered. In general a single dose of 0.5 to 1gm is considered maximum**.**

1. Ionization, pka & Aqueous Solubility

The pH Partition hypothesis simply states that the unchanged form of a drug species will be preferentially absorbed through many body tissues. Therefore it is important to note the relationship between the pKa of the compound and its absorptive environment. For many compounds, the site of maximum absorption will also be the area in which the drug is least soluble**.**

3. Partition coefficient

The compounds with a relatively high partition coefficient are predominantly lipid soluble and easily penetrate membranes resulting high bioavailability**.** Compounds with very low partition coefficient will have difficulty in penetrating membranes resulting poor bioavailability. Furthermore, partitioning effects apply equally to diffusion through polymer membranes.

4. Drug Stability

The drugs, which are unstable in stomach, can be placed in a slowly soluble form and their release delayed until they reach the small intestine. However, such a strategy would be Determined for drugs that either are unstable in the small intestine (or) undergo extensive gut wall metabolism, as pointed out in the decrease bioavailability of some anti cholinergic drugs from controlled /sustained release formulation.

b) Biological Factors

Pharmacokinetic Characteristics

1. Biological Half-Life

Therapeutic compounds with half-life less than 8 hrs are excellent candidates for sustained release preparations. Drugs with very short half-life (less than 2 hrs) will require excessively large amounts of drug in each dosage unit to maintain controlled effects. Thus forcing the dosage form itself to become too large to be administered. Compounds with relatively long half-lives, generally greater than 8 hrs are not used in the sustained release dosage forms, since their effect is already sustained and also GI transit time is 8-12 hrs**.** So the drugs, which have long half life and short half life, are poor candidates for sustained release dosage forms[4].

2. Absorption

The characteristics of absorption of a drug can greatly affect its suitability as a sustained release product. Drugs which are absorbed by specialized transport process

(carrier mediated) and drug absorption at special sites of the gastrointestinal tract (Absorption Window) are poor candidates for sustained release products.

3. Metabolism

The metabolic conversion of a drug to another chemical form usually can be considered in the design of a sustained release system for that drug. As long as the location, rate and extent of metabolism are known and the rate constant for the process are not too large, successful sustained release products can be developed.

Pharmacodynamic Characteristics

1. Therapeutic Range

A drug candidate for controlled delivery system should have a therapeutic range wide enough such that variations in the release rate do not result in a concentration beyond this level.

2. Therapeutic Index

The release rate of a drug with narrow therapeutic index should be such that the plasma concentration attained is within the therapeutically safe and effective range. This is necessary because such drugs have toxic concentration nearer to their therapeutic range. Precise control of release rate of a potent drug with narrow margin of safety is difficult. A drug with short half-life and narrow therapeutic index should be administered more frequently than twice a day. One must also consider the activity of drug metabolites since controlled delivery system controls only the release of parent drug but not its metabolism.

2. Plasma concentration response

Drugs such as reserpine whose pharmacological activity is independent of its concentration are poor candidates for controlled release systems.

1.7 Polymers used in Sustained Release Formulations

Polymers have gained importance in pharmaceutical industry as both drug encapsulants and vehicles of drug carriage; either protecting an active agent during its passage through the body until its release, or controlling its release. Polymers in drug delivery are classified into

1.7.1 Bio-degradable polymers

- Natural: Alginates, Guar gum, Chitosan, Gelatin, Xanthan gum and Carrageenan.
- Synthetic: Polylactic acid, Polycaprolactone, Polyglycolic acid, Poly lacticglycolic acid and Polyanhydride.

1.7.2 Bio absorbable polymer: Polyethylene glycol and polyvinylpyrrolidone

1.7.3 Bio nondegradable polymers: Hydroxy propyl methyl cellulose, ethyl cellulose, Acrylic Polymers, Silicone elastomers, Poly vinyl chloride, Polyurethanes and polyethy vinyl acetate polymers.

The greatest advantage of biodegradable polymers is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body via normal metabolic pathways. However, biodegradable materials degradation by products that must be tolerated with little or no adverse reactions within the biological environment [5, 6].

1.8 Oral Drug Delivery Systems[7]

Among all routes of administration, the oral route has been most popular and successful.

Designs: Oral controlled delivery systems can be broadly divided into following categories, based on their mechanism of drug release:

1. Dissolution-controlled release
    a. Encapsulation dissolution control
    b. Matrix dissolution control
2. Diffusion-controlled release
    a. Reservoir devices
    b. Matrix devices
3. Ion exchange resins
4. Osmotic controlled release

Dissolution controlled release

Dissolution controlled release can be obtained by slowing the dissolution rate of a drug in the GI medium, incorporating the drug in an insoluble polymer, and coating drug particles or granules with polymeric materials of varying thickness. The rate limiting step for dissolution of a drug is the diffusion across an aqueous boundary layer. The solubility of the drug provides the source of energy for drug release, which is countered by the stagnant fluid diffusional boundary layer. The rate of dissolution (dm/dt) can be approximated by below.

$$dm/dt = ADS/h$$

S = Aqueous solubility of the drug concentration

A = Surface area of the dissolving particle or tablet concentration

D = Diffusivity of the drug

h = Thickness of the boundary layer.

Drug delivery using rate of dissolution as a controlled release mechanism can be achieved by encapsulation of a drug-polymer matrix with a relatively insoluble polymeric membrane. The coated beads can be compressed into tablets or capsulated, as was done with the spansule products. Since the time required for the membrane coat to dissolve is a function of membrane thickness, granules with varying thicknesses can be employed to achieve sustained release of the drug.

One of the most common approaches used to achieve sustained release is to incorporate a drug in a hydrophobic matrix such as wax, polyethylene, polypropylene and ethylcellulose; or a hydrophilic matrix such as hydroxypropylcellulose, hydroxylpropylmethylcellulose, methylcellulose and sodium carboxymethylcellulose. The rate of drug availability is controlled by the rate of penetration of the dissolution fluid into the matrix. It depends on the porosity of the compressed structure. In the case of a water-soluble drug in a hydrophobic matrix, the rate of drug availability.

Diffusion Controlled Release

Diffusion of a drug molecule through a polymeric membrane forms the basis of these controlled drug delivery systems. Similar to the dissolution controlled systems, the diffusion controlled devices are manufactured either by encapsulating the drug particle in a polymeric membrane or by dispersing the drug in a polymeric matrix. Unlike the dissolution-controlled systems, the drug is made available as a result of partitioning through the polymer. In the case of a reservoir type diffusion controlled device, the rate of drug released (dm/dt) can be calculated using below.

$$\mathbf{dm/dt = ADK\Delta C/l}$$

A = Area

D = Diffusion coefficient

K = Partition coefficient of the drug between the drug core and the membrane

l = Diffusional pathlegth and ΔC = Concentration difference across the membrane.

Another configuration of diffusion controlled systems includes matrix devices, which are very common because of ease of fabrication. Diffusion control involves dispersion of drug in either a water-insoluble or a hydrophilic polymer. The release rate is dependent on the rate of drug diffusion through the matrix but not on the rate of solid dissolution. Below describes the amount of drug released from the systems as derived by Higuchi

$$\mathbf{Q = [D\varepsilon/ \tau\ (2C - \varepsilon S)\ St]^{1/2}}$$

Q = Amount of drug released per unit surface area

D = Diffusion coefficient of the drug in the release media

ε = Porosity

τ = Tortuosity of the matrix

S = Solubility of the drug in the release media

C = Concentration of the drug in the tablet

Osmotically controlled release

In the early 1970s, Developed an elementary osmotic pump (EOP) to achieve controlled drug delivery. The delivery of the drug from the system is controlled by solvent influx across a semipermeable membrane, which in turn carries the drug outside through a laser drilled orifice. The osmotic and hydrostatic pressure differences on either side of the semipermeable membrane govern fluid transport into the system. Therefore, the rate of drug delivered from the system is dependent on the osmotic pressure of the formulation (π_s) as shown in below .

$$\mathbf{dm/dt = Ak\pi_sS/h}$$

A = Membrane area

k = Membrane permeability and h = Membrane thickness.

More recently, ALZA Corporation has developed several other controlled release technology platforms based on the original concept of osmosis across a semipermeable membrane. OROS Push-Pull technology has proven to be very useful for delivering compounds of very high or very low solubility such as Oxybutynin chloride and Nifedipine.

Ion Exchange resins

The idea of using ion exchange resins for controlled drug delivery was adapted from analytical and protein chemistry. Resins are water insoluble materials containing anionic groups such as amino or quaternary ammonium groups, cationic groups such as carboxylic groups, or sulfonic groups in repeating positions on the resin chain. A drug resin complex is formed by prolonged exposure of drug to the resin.

Theoretically this controlled delivery approach is relatively immune to the conditions of the GI tract because an ionic environment is required to displace the drug from the resin. Biphetamin, a capsule containing equal quantities of amphetamine and dextro amphetamine complexed to a sulfonic acid cation exchange resin, has been used as an antiobesity drug and for behavior control in children.

Further improvement of the ion exchange type of delivery system is illustrated by the development of the Pennkinetic system. In this system, drug containing resin granules is first treated with a polymer such as polyethylene glycol 4000 to retard the rate of swelling in water and then further coated with a water permeable polymer such as ethylcellulose to act as rate-limiting barrier to control drug release.

1.9. HYPERTENSION

Hypertension or high blood pressure is a cardiac chronic medical condition in which the systemic arterial blood pressure is elevated. What that means is that the heart is having to work harder than it should to pump the blood around the body. Blood pressure involves two measurements, systolic and diastolic. Normal blood pressure is at or below 120/80 mmHg. Hypertension is the opposite of hypotension. Hypertension is classified as either primary (essential) hypertension or secondary hypertension; about 90–95% of cases are categorized as "primary hypertension," which means high blood pressure with no obvious medical cause. The remaining 5–10% of cases (Secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart or endocrine system [8, 9].

CLASSIFICATION

Blood pressure is usually classified based on the systolic and diastolic blood pressures. Systolic blood pressure is the blood pressure in vessels during a heartbeat. Diastolic blood pressure is the pressure between heartbeats. A systolic or the diastolic blood pressure measurement higher than the accepted normal values for the age of the individual is classified as pre Hypertension .

Hypertension has several sub-classifications, including hypertension stage I, hypertension stage II, and isolated systolic hypertension. Isolated systolic hypertension refers to elevated systolic pressure with normal diastolic pressure and is common in the elderly. These classifications are made after averaging a patient's resting blood pressure readings taken on two or more office visits. Individuals older than 50 years are classified as having hypertension if their blood pressure is consistently at least 140mmHg systolic or 90 mmHg diastolic. Patients with blood pressures higher than 130/ 80mmHg with concomitant presence of diabetes mellitus or kidney disease require further treatment.

Table.No: 2

Classification of Hypertension

Classification	Systolic pressure		Diastolic pressure	
	mmHg	pKa	mmHg	pKa
Normal	90–119	12–15.9	60–79	8.0–10.5
Pre hypertension	120–139	16.0–18.5	80–89	10.7–11.9
Stage 1	140–159	18.7–21.2	90–99	12.0–13.2
Stage 2	≥160	≥21.3	≥100	≥13.3
Isolated systolic hypertension	≥140	≥18.7	<90	<12.0

Essential hypertension

Essential hypertension is the most prevalent hypertension type, affecting 90–95% of hypertensive patients. Although no direct cause has been identified, there are many factors such as sedentary lifestyle, smoking, stress, visceral obesity, potassium deficiency (hypokalemia), obesity(more than 85% of cases occur in those with a body mass index greater than salt (sodium) sensitivity, alcohol intake, and vitamin D deficiency that increase the risk of developing hypertension. Risk also increases with aging, some inherited genetic mutations, and having a family history of

hypertension. An elevated level of renin, a hormone secreted by the kidney, is another risk factor, as is sympathetic nervous system over Insulin resistance, which is a component of syndrome X (or the metabolic syndrome), is also thought to contribute to hypertension. Recent studies have implicated low birth weight as a risk factor for adult essential hypertension.

Secondary hypertension

Secondary hypertension by definition results from an identification cause. This type is important to recognize since it's treated differently to essential hypertension, by treating the underlying cause of the elevated blood pressure. Hypertension results in the compromise or imbalance of the patho physiological mechanisms, such as the hormone-regulating endocrine system, that regulate blood plasma volume and heart function. Many conditions cause hypertension. Some are common, well recognized secondary causes such as renovascular hypertension and Cushing's syndrome, which is a condition where the adrenal glands overproduce the hormone cortisol. Hypertension is also caused by other conditions that cause hormone changes, such as hyperthyroidism, hypothyroidism, and certain tumors of the adrenal medulla (e.g., pheochromocytoma). Other common causes of secondary hypertension include kidney disease, obesity and certain prescription and illegal drugs.

Pathophysiology

Most of the mechanisms associated with secondary hypertension are generally fully understood. However, those associated with essential (primary) hypertension are far less understood. What is known is that cardiac output is raised early in the disease course, with Total Peripheral Resistance (TPR) normal over time cardiac output drops to normal levels but TPR is increased. Three theories have been proposed to explain this

- Inability of the kidneys to excrete sodium, resulting in nutriuretic factors such as being secreted to promote salt excretion with the side effect of raising total peripheral resistance.

- An overactive renin-angiotensin system leads to vasoconstriction and retention of sodium and water. The increase in blood volume plus vasoconstriction leads to hypertension.
- An overactive sympathetic nervous system, leading to increased stress responses. It is also known that hypertension is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have been postulated in the etiology of this condition.

Drug treatment in Hypertension[8,]

When lifestyle measures and supplements are not enough to cure the condition, medical treatment must be applied. Many different types of drugs are used, alone or in combination with other drugs, to treat high blood pressure. The major categories are

- **Angiotensin-converting Enzyme (ACE) Inhibitors:** ACE inhibitors work by preventing a chemical in the blood, angiotensin I, from being converted into a substance that increases salt and water retention in the body. These drugs also make blood vessels relax, which further reduces blood pressure.

  Examples: Captopril,Ramipril

- **Angiotensin II Receptor Antagonists:** These drugs act at a later step in the same process that ACE inhibitors affect. Like ACE inhibitors, they lower blood pressure by relaxing blood vessels.

  Examples: Losartan,Valsartan.

- **Beta blockers:** Beta blockers affect the body's response to certain nerve impulses. This, in turn, decreases the force and rate of the heart's contractions, which lowers blood pressure.

  Examples: Atenolol,Metaprolol.

- **Blood Vessel Dilators (Vasodilators):** These drugs lower blood pressure by relaxing muscles in the blood vessel walls.

  Examples: Minoxidil,Hydralazine.

- **Calcium Channel Blockers:** Drugs in this group slow the movement of calcium into the cells of blood vessels. This relaxes the blood vessels and lowers blood pressure.

  Examples: Amlodipine,Diltiazem

- **Diuretics:** These drugs control blood pressure by eliminating excess salt and water from the body.

  Examples: Furosemide,Spironolactone

- **Nerve Blockers**: These drugs control nerve impulses along certain nerve pathways. This allows blood vessels to relax and lowers blood pressure.

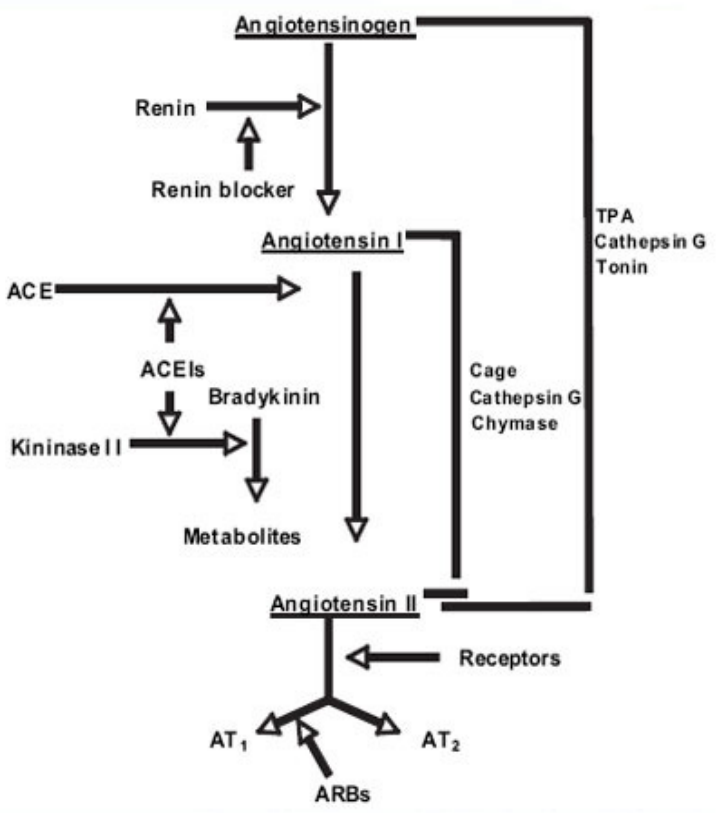
  Examples: Reserpine, Gaunithidine.

Ideal Properties of an Antihypertensive Agent

- Controls blood pressure by acting on the pathophysiological mechanisms that raise blood pressure.
- It should be effective i.e. produce significant lowering of blood pressure; both systolic and diastolic.
- Early onset of action.
- Sustained lowering of blood pressure for 24hours no early morning risk.
- Synergistic in blood pressure lowering effects when combined with other agents.
- Good clinical tolerability profile thus increased patient compliance.
- Vascular protection of end organs.
- Pleiotropic benefits.
- Safe for long term use absence of deleterious metabolic effects.

- Administation indicated in hypertensive patients with associated or concomitant pathology.

Fig No:2 Mechanism of action of angiotensin II receptor blockers



These drugs block the action of angiotensin II at receptor level.

They act by blocking the angiotensin II receptors of subtype1 which regulates the effects of angiotensin II on blood pressure, heart, on sodium and water balance. By blocking the receptors these drugs inhibit the actions of angiotensin II and produse the following effects

- Vasodilation and consequent decrease in peripheral vascular resistance
- Decreased retention of sodium and water due to decrease in aldosterone synthesis.
- Decreased release of vasopressin which is an Antidiuretic hormone and a vasoconstrictor. All these effects leads to fall in elevated Blood pressure.
- Decrease in cardiovascular hypertrophy.

2. LITERATURE REVIEW

K. Raghuram Reddy et.al.,(2003) The objective of the present study was to develop once daily sustained release matrix tablets of nicorandil, a novel potas-sium channel opener used in cardiovascular diseases. The tablets were prepared by the wet granulation method. Etha-nolic solutions of ethylcellulose (EC), Eudragit RL-100, Eudragit RS-100, and polyvinylpyrrolidone were used as granulating agents along with hydrophilic matrix materials like hydroxypropyl methylcellulose (HPMC), sodium car-boxymethylcellulose and sodium alginate. The granules were evaluated for angle of repose, bulk density, compressi-bility index, total porosity, and drug content. The tablets were subjected to thickness, diameter, weight variation test, drug content, hardness, friability, and in vitro release studies. The granules showed satisfactory flow properties, compressibility, and drug content[9].

Chinam Niranjan Patra et.al., (2007) evaluated the objective of the present research was to develop a bilayer tablet of propranolol hydrochloride using superdisintegrant sodium starch glycolate for the fast release layer and water immiscible polymers such as ethylcellulose, Eudragit RLPO and Eudragit RSPO for the sustaining layer. *In vitro* dissolution studies were carried out in a USP 24 apparatus I. The formulations gave an initial burst effect to provide the loading dose of the drug followed by sustained release for 12 h from the sustaining layer of matrix embedded tablets. *In vitro* dissolution kinetics followed the Higuchi model via a non-Fickian diffusion controlled release mechanism after the initial burst release. FT-IR studies revealed that there was no interaction between the drug and polymers used in the study[10].

C.P. Jain et.al., (2009) In this investigation fast dissolving tablets of valsartan were prepared using different superdisintegrants by direct compression method. FDTs were evaluated for physicochemical properties and *in vitro* dissolution. Effect of disintegrant on disintegration behaviour of tablet in artificial saliva, pH 5.8 was evaluated. Wetting time of formulations containing Crospovidone was least and tablets showed fastest disintegration. The drug release from FDTs increased with increasing concentration of superdisintegrants and was found to be highest with formulations containing Crospovidone. The release of valsartan from FDTs was found to follow non-Fickian diffusion kinetics[11].

George Vamvakas et.al., (2010) Valsartan is a non-peptide, orally active and specific angiotensin receptor blocker with particularly high affinity for the type I (AT1) receptor subtype. Diovan is available as tablets for oral administration. Absolute bioavailability for Diovan is 25%(range 10-35%)1. Also, the intra-subject variability is 60%1. A novel SEDDS based formulation for Valsartan was developed, which is a combination of Valsartan with high HLB oil, high HLB surfactants and co-solvent. In vitro data indicated greater release of the drug from the dosage form compared to Diovan tablets. It was therefore of interest to evaluate the formulations in an in vivo pilot clinical study against Diovan. The data indicated that Banner's SEDDS based formulation for Valsartan gave higher systemic exposure and lower variability results compared to Diovan[12].

Abdel Naser Zaid et.al., (2010) assess the quality of Valzan tablet (160 mg,valsartan immediate release test formulation) by comparing its pharmacokinetic parameters with Diovan tablet (160 mg, valsartan reference formulation). Valzan tablets were prepared according to a dry granulation method (roll compaction). To assess the bioequivalence of Valzan tablets a randomized, two-way, crossover, bioequivalence study was performed in 24 healthy male volunteers.. Based on this statistical evaluation it was concluded that the test tablets (Valzan) is well formulated, since it exhibits pharmacokinetic profile comparable to the reference brand Diovan[13].

S. Indumathy et. al., (2010) evaluated valsartan for its action on inflammation using plethysmograph method i.e. carageenin induced paw edema model. It was reported that angiotensin II generated from plasma had various effects including inflammation. It stimulates the release of pro inflammatory cytokines, activates Nuclear factor kappa B (NF – kB), increases oxidant stress, suppress nitric oxide synthesis and behave as an inflammatory molecule. It also induces inflammation through the production of reactive oxygen species, adhesion molecules, and inflammatory cytokines such as chemo attractant protein-1(MCP-1).our study showed that the tested drugs of angiotensin antagonists at a dose of 10mg/Kg possessed significant anti inflammatory activity[14].

Parikh Bhavik Anjankumar et.al., (2010) design and evaluate mucoadhesive bi-layered buccal devices comprising a drug containing mucoadhesive layer and a drug free backing membrane. Bi laminated films composed of mixture of drug (Valsartan) and chitosan, with hydroxylpropylmethylcellulose (15 cps) and backing layer (ethyl cellulose). Films were fabricated by solvent casting technique and were evaluated for thickness, drug content uniformity, bio-adhesion strength, percent, swelling index, folding endurance and in vitro drug release. A combination of chitosan and hydroxylpropylmethylcellulose (1:1) using propylene glycol (50% by weight of polymer) as plasticizer gave promising results. The optimized film exhibited an In vitro drug release of approximately 90% in 5 hrs along with satisfactory bio-adhesive strength[15].

K. Venkates Kumar et.al., (2010) worked out an attempt to improve the solubility and dissolution rate of a poorly soluble drug, Valsartan by solid dispersion method using skimmed milk powder as carrier. Four different formulations were prepared with varying drug: carrier ratios viz.1:1, 1:3, 1:5 and 1:9 and the corresponding physical mixtures were also prepared. The formulations were characterized for solubility parameters, drug release studies and drug-polymer interactions by using phase solubility studies, dissolution studies; XRD analysis, FTIR spectrum, TLC analysis and UV overlay spectra. All the formulations showed marked improvement in the solubility behavior and improved drug release. Formulation containing drug:polymer ratio of 1:9 showed the best release with a cumulative release of 81.60% as compared to 34.91 % for the pure drug. The interaction studies showed no interaction between the drug and the carrier[16].

Carlos Eduardo De Matos Jensen et. al., (2010) Valsartan, a water-insoluble drug, is mainly used in the treatment of hypertension with reduced oral bioavailability. The aim of work was to develop a valsartan:β-cyclodextrin (VAL:β-CD) pharmaceutical composition in order to improve its water solubility and bioavailability. The VAL:β-CD complexes were prepared by the kneading, solid dispersion and freeze-drying methods, of which the freeze-drying method(FDY) was found to be the best to prepare an inclusion complex. A physical mixture PM was also prepared. Complexes were characterized by thermal analysis, Fourier transformed- infrared (FTIR) spectroscopy, Powder X-ray diffractometry, intrinsic dissolution and NMR (2D-ROESY). Phase-solubility analysis showed AL-type diagrams

with β-cyclodextrin (β-CD). Micro calorimetric titrations suggested the formation of 1:1inclusion complex between VAL and β-CD. The apparent stability constants *K*1:calculated from phase-solubility plots were 165.4 M-1 (298 K), 145.0 M-1 (303 K) and111.3 M-1 (310 K)[17].

D. Srinivas et.al., (2011) The purpose of the present work is to formulate and evaluate of Valsartan film coated tablets. In order to obtain the best optimized product, eight different formulations were developed using diluents, binder, glidant, lubricant, and different concentrations of superdisintegrant. Tablets were formulated by direct compression, slugging and wet granulation techniques. Various pre-compressional parameters like bulk density, tapped density, compressibility index and Hausner's ratio and post compressional parameters like weight variation, thickness, hardness, friability,disintegration time, and drug release were studied. Comparatively granulation techniques exhibited the good powder flow than direct compression technique. The formulation F-7 was showed good drug release and selected as an optimized formulation and it was concluded that superdisintegrant concentration, granulation technique, binder, and lubricants plays a key role in the formulation developmentand optimizing the immediate release tablet of Valsartan formulation[18].

Agnivesh R. Shrivastava et.al., (2011) present work undertaken was to enhance the solubility and dissolution rate of valsartan a poorly water soluble antihypertensive, by preparation of solid dispersion granules which would additionally allow easy compression into tablets. The dispersion granules were prepared using a hot melt granulation technique which involved preparation of a homogenous dispersion of valsartan in gelucire-50/13 melt, followed by its adsorption on to the surface of aeroperl-300pharma®, an inert adsorbent. The formulation was further characterized by FTIR, DSC, XRD and SEM analysis. FTIR spectrum revealed some drug excipient interactions. DSC and XRD data indicated the retention of amorphous form of valsartan. The *in-vitro* dissolution rate of these tablets was significantly better in comparison with marketed formulation[19].

P. Mahajan et.al., (2011) The present study was aimed to develop antihypertensive sustained release matrix tables of valsartan Angiotensin II receptor antagonist, using

hydroxypropylmethylcellulose alone and in combination with ethyl cellulose as the matrix material in different proportion by wet granulation method. The granules were evaluated for angle of repose, bulk density and Compressibility index. The tablets were subjected to weight variation test, drug content, hardness, friability, and in vitro release studies. The granules showed satisfactory flow properties, compressibility, and all the tablet formulations showed acceptable pharmacotechnical properties. The formulated tablets also compared with a marketed product. In vitro dissolution studies indicate that EC significantly reduced the rate of drug release compared to HPMC. But no significant difference was observed in the release profile of matrix tablets made by higher percentage of EC. The result of dissolution study indicate that the formulation prepared by low viscosity grade HPMC (H1and H2) showed maximum drug release up to 8 hrs and high viscosity grade HPMC and EC formulation (H3 to H6) showed upto 12 hrs[20].

M. Soumya et.al., (2011) developed and optimized bilayered sustained release matrix tablets of Valsartan. The tablets contained an immediate releasing layer with the loading dose of the drug and a sustaining layer with maintenance dose of drug prepared by wet granulation method. The immediate releasing layer is directly compressed on to the sustaining layer. Sodium starch glycholate was used as super disintegrant and Eudragit RSPO and Eudragit RLPO were used as polymers. The drug polymer interaction was investigated by FTIR and DSC and their results directed further course of formulation. Valsartan tablets were evaluated for various post compression parameters like Tablet hardness, Friability, Weight variation, Drug content and In vitro dissolution. The results were found to be within the acceptable limits. A 3^2 full factorial design was applied to systematically optimize the drug release profile. The amounts of Eudragit RSPO (X1) and Eudragit RLPO (X2) were selected as independent variables. The time required for 90% drug dissolution was selected as dependent variable[21]

K. Anjan Mahapatra et.al., (2011) Solid dispersions (SDs) and physical mixtures (PMs) of valsartan in β-cyclodextrin (β-CD), hydroxypropyl β-cyclodextrin(HP β-CD), and polyvinyl pyrollidone (PVP K-30) were prepared to increase its solubility characteristics. The drug formulations were characterized in the solid state by Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). By these physical determinations,

drug–polymer interactions were found. Both the solubility and the dissolution rate of the drug in these formulations were increased. Drug contents were determined by UV spectrophotometry at a λmax of 249.5 nm. The phase solubility behavior of valsartan in various concentrations of β-CD, HP β-CD, and PVP K-30 (0.25–1.0% w/v) in distilled water was obtained at 37 ± 2 °C. The dissolution of valsartan is increased with increasing amounts of the hydrophilic carriers (i.e., β-CD, HP β-CD, and PVP K-30). The SDs of valsartan with β-CD and HP β-CD were prepared at 1:1, 1:3, and 1:5 drug/carrier ratios by a kneading method, and PVP K-30 SDs were prepared at the same ratios (i.e., 1:1, 1:3 and 1:5 drug/carrier) by a lyophilization technique. The FTIR spectroscopic studies show the stability valsartan and the absence of well-defined drug–polymer interaction[22].

Mandadi Sunitha et.al., **(2011)** establish Bilayer tablets containing combination of valsartan as sustained release and hydrochlorothaiazide as immediate release layer. Sustained release were prepared by wet granulation method using different viscosity grades of HPMC(HPMCK4M and HPMCK50M) as polymers and immediate release were prepared by wet granulation method using superdisintergrants such as crospovidone and croscarmellose sodium. The tablets were evaluated for physiochemical properties. All the values were found to be within the limits. In vitro release studies were carried out by USP type-2 paddle apparatus. The results showed that combinations of polymers namely HPMCK4M and HPMCK50M in sustained layer can control the release of drug. The line of best fit obtained was first order release kinetics(R=0.998)and Hixon-Crowell model(R=0.995)Based on Korsmeyer-peppas model, the drug release data further analyzed for curve fitting and the results confirmed that the formulation followed non-fickian diffusion kinetics[23].

KPR. Chowdary et.al., (2011) The objective of the study is to evaluate the individual main and combined (or interaction) effects of β cyclodextrin (βCD) and surfactant (Poloxamer 407) on the dissolution rate of valsartan from CD complexes and from their tablet formulations in a series of 22 factorial experiments. Solid inclusion complexes of Drug- βCD were prepared with and without Poloxamer 407 by kneading method as per 22-factorial design and were evaluated for dissolution rate and efficiency. The feasibility of formulating valsartan- βCD - Poloxamer 407 solid inclusion complexes into tablets was also evaluated. To evaluate the individual and combined effects of βCD and Poloxamer 407 on the

dissolution rate of valsartan tablets, tablets each containing 40 mg of valsartan were formulated employing inclusion complexes of drug- βCD - Poloxamer 407 as per 22 factorial design. All the prepared tablets were evaluated for hardness, friability and disintegration time and dissolution rate of valsartan[24].

Sh. Lakade et.al., **(2011)** The present study aimed to develop hydrophilic polymer (HPMC) and hydrophobic polymer (Ethyl cellulose) based Nicorandil matrix sustained release tablet which can release the drug up to time of 24 hrs in predetermined rate. The formulation of Nicorandil matrix tablet was prepared by the polymer combination in order to get required theoretical release profile. The influence of hydrophilic and hydrophobic polymer and granulation technique on Nicorandil was studied. The formulated tablet were also characterized by physical and chemical parameters, The in-vitro release rate profile should the higher concentration of F2 polymer in tablet, the combination of hydrophilic and hydrophobic combination showed less result than use of alone[25].

G. Raghavendra rao et. al., (2011) develop sustained release matrix tablets of water soluble Tramadol hydrochloride using different polymers viz. Hydroxy propyl methyl cellulose (HPMC) and natural gums like Karaya gum (KG) and Carrageenan (CG). Varying ratios of drug and polymer like 1:1 and 1:2 were selected for the study. After fixing the ratio of drug and polymer for control the release of drug up to desired time, the release rates were modulated by combination of two different rates controlling material and triple mixture of three different rate controlling material. After evaluation of physical properties of tablet, the *in vitro* release study was performed in 0.1 N HCl pH 1.2 for 2 hrs and in phosphate buffer pH 6.8 up to 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. Different ratios like 80:20, 60:40, 50:50, 40:60 and 20:80 were taken. Dissolution data was analyzed by Korsmeyer-Peppas power law expression and modified power law expression. It was observed that matrix tablets contained polymer blend of HPMC/CG were successfully sustained the release of drug upto 12 hrs[26].

Gulam Irfani et.al., (2011) In the present work, Transdermal drug delivery of valsartan were formulated in different concentration (10%, 20% and 30%) of glycerin as plasticizer and a blend of two in different concentrations of polymers (PVPK30, HPMC and Eudragit RS 100)

were formulated by solvent casting method. Drug polymer interaction study was carried out using FTIR. Other characteristics were confirmed by XRD and SEM studies. The formulated valsartan patches exhibited good physicochemical characteristics. *In-vitro* diffusion studies were performed in phosphate buffer pH 7.4 at λ max 260nm, by using cellophane membrane (0.45µ) in an artificial Keshary chein diffusion cell. In this study the results indicates, as increase in the concentration of glycerin, increases the diffusion rate of valsartan patches. Among polymers, the combination of Eudragit RS 100 with HPMC had increased diffusion rate. Various pre-compressional parameters like bulk density, tapped density, compressibility index and Hausner's ratio and post compressional parameters like weight variation, thickness, hardness, friability,disintegration time, and drug release were studied. Comparatively granulation techniques exhibited the good powder flow than direct compression technique.. The formulation F-7 was showed good drug release and selected as an optimized formulation and it was concluded that superdisintegrant concentration, granulation technique, binder, and lubricants plays a key role in the formulation development and optimizing the immediate release tablet of Valsartan formulation[27].

3. AIM AND OBJECTIVE

To design, formulate and evaluate sustained release tablets of Valsartan sodium which is expected to deliver the drug in controlled and sustained release manner with reduce frequency of drug administration, reduce GI tract side effects and improve patient compliance.

The half life of Valsartan is about 5-8 hrs. So a controlled release formulations of Valsartan would increase the length of time release in which Valsartan acheives an effective concentration in the body.

The present work is aimed at preparation and evaluation of Sustained Release matrix tablets of Valsartan sodium using different polymers.

To sustain the release and maintain the therapeutic concentration. by reducing the dose to 160 mg. To formulate and evaluate matrix tablets of Valsartan to sustain the release of drug for 12 hrs. Evaluation of optimized tablets. To improve the oral bioavailability and to reduce the dose dependent toxicity there is a need for the development of sustained-release formulations.

4. PLAN OF WORK

The following experimental protocol was therefore designed to allow a systemic approach to the study.

1. Selection of drug and excipients.

2. Identification of drugs by *FTIR*

3. Preformulation study

4. Compatibility study

5. Preparation of standard curve

6. Formulation development

In Process Evaluation

- Angle of Repose
- Apparent Bulk Density
- Tapped Density
- Loss on drying
- Hausner's ratio
- Carr's index.

Evaluation of Final Product

- Tablet thickness
- Tablet hardness
- Friability
- Weight variation
- Disintegration.

7. In-vitro dissolution study

8. Stability studies

MATERIALS AND METHODS

Table No: 3

5.1 Materials used

S.No.	Chemicals	Company
1	Valsartan sodium	Dr Reddys laboratories, Hyderabad
2	HPMC	Oxford Laboratories, Mumbai
3	Kollidon	Indian Research Products, Chennai
4	Ethyl cellulose	Oxford Laboratories, Mumbai
5	Talc	S.D. Fine Chem. Ltd, Mumbai
6	Magnesium stereate	S.D. Fine Chem. Ltd, Mumbai
7	Micro crystalline Cellulose	S.D. Fine Chem. Ltd, Mumbai

Table 5.2 List of equipments used in this study

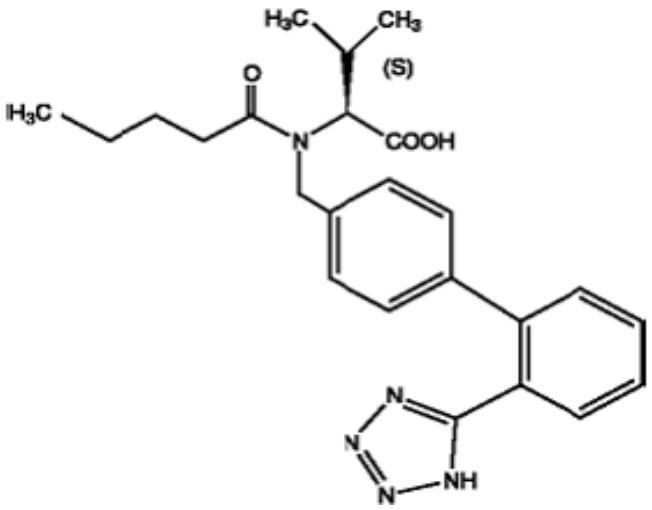
S.NO.	Equipment	Company
1	16 station Compression Machine	Cadmach Machinery, Ahmedabad.
2	Balance	Mettler Toledo, Germany.
3	Hardness Tester	Pharma test, Ahmedabad.
4	Dissolution Apparatus, USP	Electrolab, Mumbai.
5	UV-Visible Spectrophotomter	Varian Cary C50 Conc, Germany.
6	Friability Tester	Electrolab, Mumbai.
7	Tap Density Tester (USP)	Electrolab, Mumbai.
8	Vernier Calipers	Mitutoyo, Japan.

5.3. DRUG PROFILE

Valsartan sodium[28]

Valsartan is a nonpeptide, orally active, and specific angiotensin II receptor blocker acting on the AT_1 receptor subtype.

1. **Chemical Name** : Valsartan is chemically described as N-(1-oxopentyl)-N-[[2'-(1H- tetrazol-5-yl) [1,1'-biphenyl]-4-yl]methyl]-L-valine.
2. **Molecular Formula** : $C_{24}H_{29}N_5O_3$
3. **Molecular weight** : 435.5
4. **Chemical Structure** :



5. **Category** : Anti hypertensive
6. **Appearance** : Valsartan is a white to practically white fine powder
7. **Solubility** : It is soluble in ethanol and methanol and slightly soluble in water.
8. **Melting Point** : The melting point was found to be 178^0C.
9. **Storage** : Store at 25°C Protect from moisture

Pharmacokinetics

1. **Dose** : 160 mg daily twice
2. **Onset of action** : 3hrs
3. **Volume of distribution** : The volume of distribution is approximately 17 L.
4. **Excretion** : Valsartan, when administered as an oral solution, is primarily recovered in feces about 83% of dose and urine about 13% of dose.
5. **Plasma Protein binding** : 95% bound to plasma proteins
6. **Bioavailability** : The systemic bioavailability is approximately 46%
7. **Elimination half life** : The plasma elimination half-life is approximately 5-8 hrs.
8. **Mechanism of Action** : Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Diovan (valsartan) blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

5.4 EXCIPIENT PROFILE

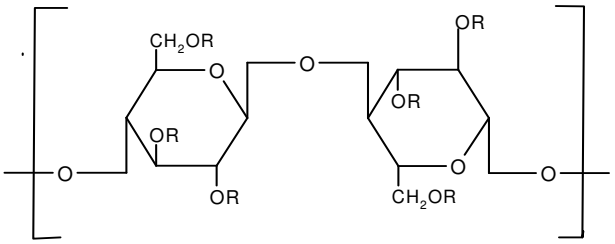
5.4.1 HYDROXY PROPYL METHYL CELLULOSE [29]

Hydroxy propyl methylcellulose is mixed Alkyl hydroxyl alkyl cellulose ether and may be regarded as the propylene glycol ether of methylcellulose.

1. Chemical Name : Cellulose, 2-hydroxypropyl methyl ether

2. Synonyms : Methyl Hydroxy Propyl Cellulose, Propylene glycol ether of methylcellulose, Culminal HPMC.

3. Structural Formula:



Where R is H, CH_3 or CH_3-CH(OH)-CH_2

4. Physical and chemical properties

5. Molecular weight : 10,000 - 15,00,000

6. Color : White to creamy-white

7. Nature : Fibrous or granular powder

8. Odour : Odourless

9. Taste : Tasteless

10. Density : 0.3-1.3 g/ml

11. Specific gravity : 1.26

12. Solubility : Soluble in cold water, practically insoluble in Chloroform, ethanol (95%) and ether but Soluble in mixture of ethanol and Dichloromethane.

13. Melting point : 190-200 °C,

14. Functional Category

Coating agent, film-forming, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

15. Application

In oral product HPMC is primarily used as tablet binder, in film coating and as an extended release tablet matrix. Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation process. High viscosity grade may be used to retard the release of water-soluble drug from a matrix.

HPMC is widely used in oral and topical pharmaceutical formulation. Concentration of 0.45-1% w/w may be added as a thickening agent to vehicle for eye drop and artificial tear solution. HPMC is used as an adhesive in plastic bandage and as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products.

In addition, HPMC is used as an emulsifier, suspending agent and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particle from coalescing or agglomerating thus, inhibiting the formation of sediments.

16. Stability and storage

It is stable although it is slightly hygroscopic. The bulk material should be stored in an airtight container in a cool and dry place. Increased in temperature reduces the viscosity of the solution.

5.4.2 Vinyl pyrrolidone vinyl acetate [30]

Poly vinylacetate/Povidone based polymer (Kollidon SR) is a relatively new extended release matrix excipient. It consists of 80% Poly vinyl acetate and 19% Povidone in a physical mixture, stabilized with 0.8% sodium lauryl sulfate and 0.2% colloidal silica.

1. **Synonyms** : E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; poly vinyl pyrrolidone; PVP; 1-vinyl-2-pyrrolidinone polymer.
2. **Chemical name** : Vinylpyrrolidone-vinyl acetate
3. **Description** : It is a tasteless, free-flowing, non-hygroscopic, white powder.
4. **Functional Category** : Direct compressible grade sustained release matrix former.
5. **Angle of Repose** : 21°
6. **Bulk Density** : 0.37 g/ml
7. **Tapped Density** : 0.44 g/ml
8. **Hausner's Ratio** : 1.13
9. **Mean Particle Size** : Approx. 100 μm
10. **Uses** : It can be easily applied for controlled release properties by direct compression. It favours the development and manufacture of Sustained release tablets by its high dry binding capacity and the superb flow properties. It offers a reliable sustained release characteristic independent of the drug used. By applying low compression force floating tablets with longer residence time in the stomach can be achieved.

5.4.3 Ethyl cellulose [31]

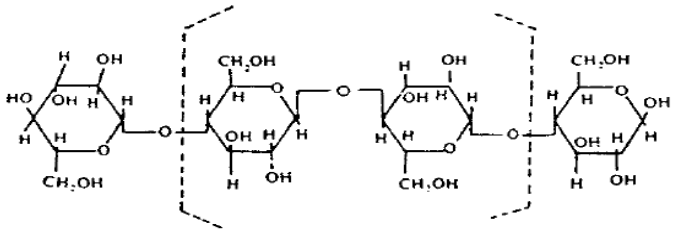
Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of β-anhydro glucose units joined together by acetal linkages.

1. **Synonyms** : Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.
2. **Description** : It is a tasteless, free-flowing, white to light tan-colored powder.
3. **Functional Category** : Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.
4. **Solubility** : It is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%). Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.
5. **Stability and Storage:** It is a stable, slightly hygroscopic material. It should be stored at a temperature not exceeding 32°C (90°F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.
6. **Safety** : It is generally regarded as a nontoxic, nonallergenic, and nonirritating material. It is not metabolized following oral consumption and is therefore a noncalorific substance.
7. **Uses** : It is used in the microencapsulation (10-20% w/w).
   - **a.** As a sustained-release tablet coating (3-20% w/w).
   - **b.** It can be used for tablet coating and tablet granulation

5.4.4 Microcrystalline cellulose[32]

Microcrystalline cellulose is purified, partially depolymerized cellulose.

1. **Synonyms** : Avicel P^H; Celex; cellulose gel; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; Tabulose; Vivapur.



2. **Description** : It occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.
3. **Grades** : Avicel P^H-101, P^H-102, P^H-103; Emcocel 50M, 90M; Vivapur 101, 102.
4. **Functional Category:** Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.
5. **Solubility** : Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.
6. **Melting point** : Chars at 260-270°C.
7. **Stability and Storage:** It is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.
8. **Safety** : It is a relatively nontoxic and nonirritant material.
9. **Uses** : It is widely used as a diluent (20 – 90 %w/w).
    a. As a tablet disintegrant (5-15% w/w).
    b. It can be used as an adsorbent, antiadherent (20-90%w/w).

5.4.5 Talc [33]

Talc is a purified, hydrated and magnesium silicate.

1. **Synonyms** : Altalc; E553b; Hydrous magnesium calcium silicate; Hydrous magnesium silicate; Luzenac Pharma; Magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; Powdered talc; Purified French chalk; Purtalc; Soapstone; Steatite; Superiore.
2. **Description** : Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.
3. **Functional Category** : Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.
4. **Solubility** : Practically insoluble in dilute acids and alkalis, organic solvents, and water.
5. **Stability and Storage:** Talc is a stable material and may be sterilized by heating at 160°C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. It should be stored in a well-closed container in a cool, dry place.
6. **Safety** : Talc is used mainly in tablet and capsule formulations. It is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However, intranasal or intravenous abuse of products containing talc can cause granulomas in body tissues, particularly the lungs. Contamination of wounds or body cavities with talc may also cause granulomas; therefore, it should not be used to dust surgical gloves. Inhalation of talc causes irritation and may cause severe respiratory distress in infants.
7. **Incompatibilities** : Incompatible with quaternary ammonium compounds.
8. **Uses** : Talc can be used in oral solid dosage formulations as a

lubricant and diluent. However, it is widely used as a dissolution retardant in the development of controlled-release products. It is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets; and as an adsorbent. In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

5.4.6 Magnesium Stearate [34]

1. **Synonyms** : Magnesium octadecanoate; Octadecanoic acid, magnesium salt; Stearic acid, magnesium salt.
2. **Functional Category** : Tablet and capsule lubricant.
3. **Description** : It is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.
4. **Flowability** : Poorly flowing, cohesive powder.
5. **Melting range** : 117–150°C (commercial samples);
6. **Solubility** : Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
7. **Stability and Storage:** It is stable and should be stored in a well-closed container in a cool, dry place.
8. **Incompatibilities** : Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials. It cannot be used in products containing aspirin, some vitamins, and most alkaloidal salts.
9. **Safety** : Nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.
10. **Uses** : It is widely used in cosmetics, foods, and pharmaceutical formulations.

5.5. PREFORMULATION STUDY[35]

Standard Graph of Valsartan Sodium

Accurately weighed amount of 100 mg Valsartan Sodium was transferred into a 100ml volumetric flask. 20 ml of 0.1N hydrochloric acid (HCl) was added to dissolve the drug and volume was made up to 100 ml with the same HCl. The resulted solution had the concentration of 1mg/ml which was labeled as 'stock'. From this stock solution 10ml was taken and diluted to 100 ml with 0.1N HCl which has given the solution having the concentration of 100 mcg/ml. Necessary dilutions were made by using this second solution to give the different concentrations of Valsartan Sodium (5 to 50 mcg/ml) solutions[35].

The absorbances of above solutions were recorded at λ_{max} (249 nm) of the drug using double beam UV-Visible spectrophotometer. Standard graph was plotted between the concentration (on X-axis) and absorbance (on Y-axis). Similarly, standard graph was plotted with 6.8 pH phosphate buffer.

Preparation of 0.1 N HCl: Accurately measured 8.5 ml of concentrated hydrochloric acid was added to 1000 ml of distilled water.

Preparation of pH 6.8 phosphate buffer: Accurately measured 50 ml of 0.2 M potassium dihydrogen phosphate was transferred to a 200ml volumetric flask and 22.4 ml of 0.2 M sodium hydroxide was added to it. Volume was made up to 200 ml with distilled water, mixed and pH was adjusted to 6.8 with 0.2 M sodium hydroxide.

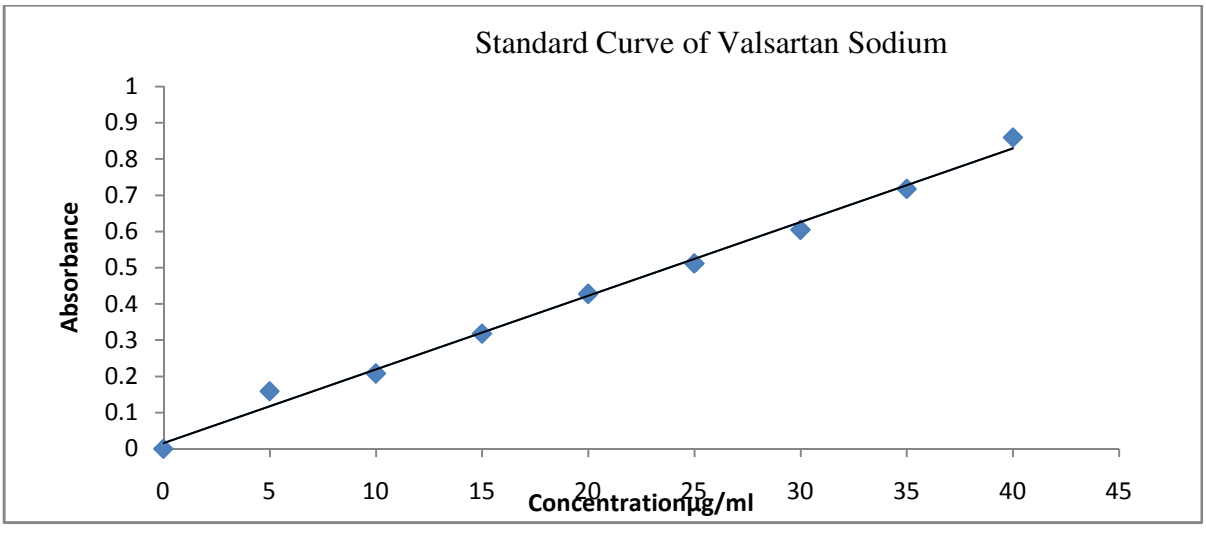
Preparation of 0.2 M potassium dihydrogen phosphate solution: Accurately weighed 27.218 g of monobasic potassium dihydrogen phosphate was dissolved in 1000 ml of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 g of sodium hydroxide pellets were dissolved in 1000 ml of distilled water and mixed.

Table No: 5 Standard Graph of Valsartan Sodium

S. No	CONCENTRATION(µg/ml)	ABSORBANCE
1	5	0.159
2	10	0.208
3	15	0.318
4	20	0.428
5	25	0.512
6	30	0.605
7	35	0.718
8	40	0.860
9	45	0.932
10	50	1.009

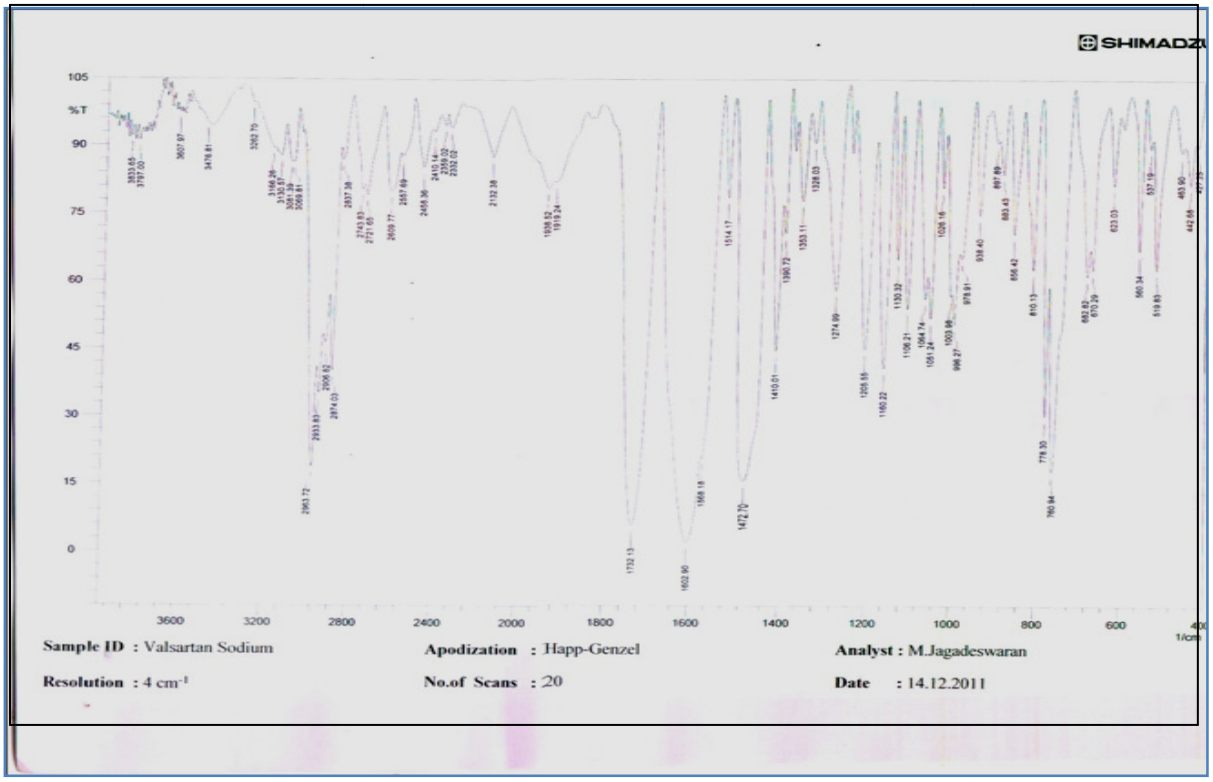
Graph No: 1 Standard graph of Valsartan Sodium



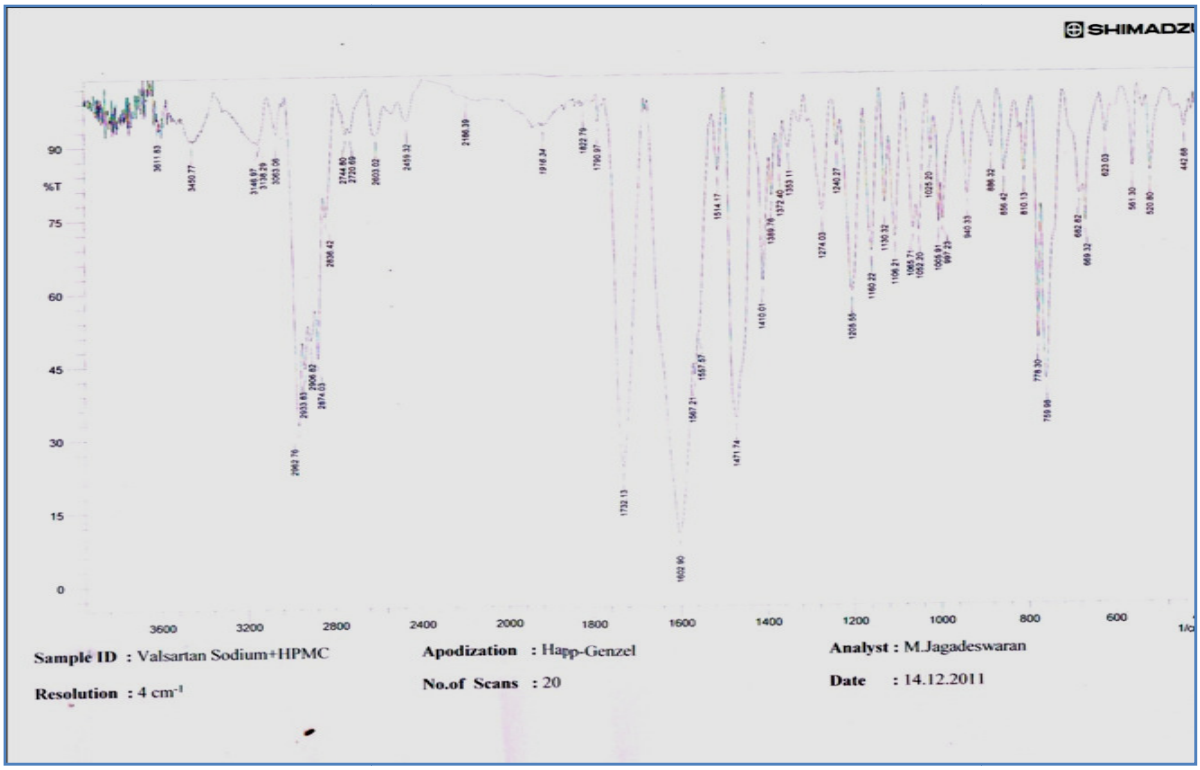
FTIR Spectra of Valsartan Sodium

The FTIR analysis of Valsartan Sodium the was carried out for qualitative compound identification. The FTIR spectra for pure drug and with other excepients was obtained by placing the drug directly into the cavity and was determined by FTIR spectrophotometer in the wave number region of 4000-400 cm^{-}

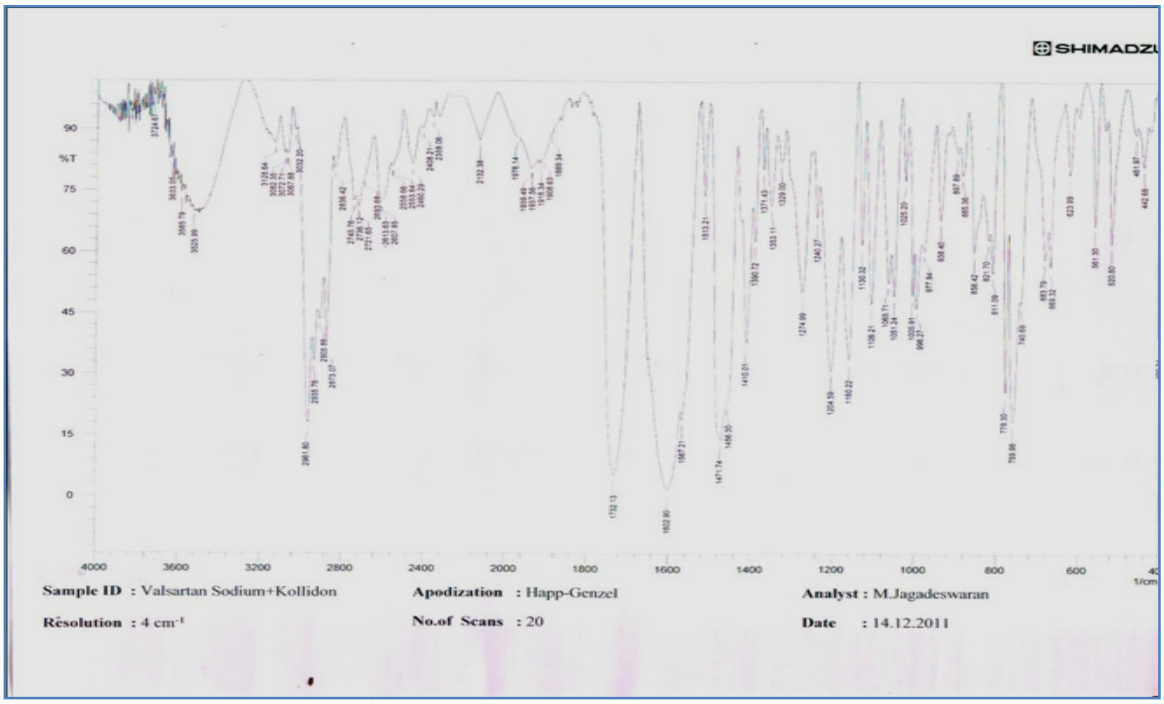
Graph No: 2 *FTIR* Spectra of Valsartan Pure Drug



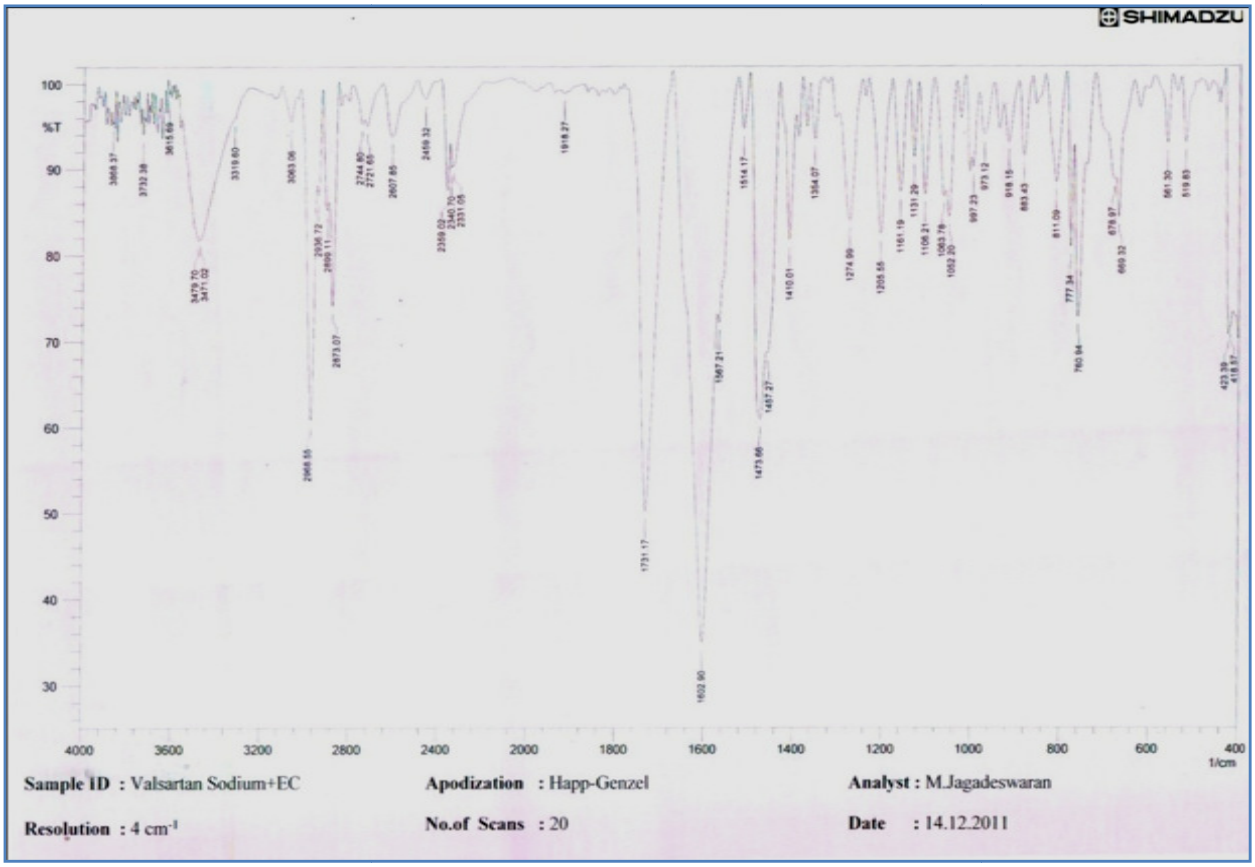
Graph No: 3 *FTIR* Spectrum of Valsartan along with HPMC



Graph No: 4 *FTIR* Spectrum of Valsartan along with Vinylpyrolidone vinyl acetate



Graph No: 5 *FTIR* Spectrum of Valsartan along with Ethyl cellulose



6. FORMULATION

6.1. Preparation of tablets

The hydrophilic matrix tablets were prepared by either direct compression or wet granulation technique. In the direct compression, sustained-release matrix tablets were formulated to contain 160 mg of Valsartan sodium. The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparation. Then add Microcrystalline cellulose was incorporated as filler excipients to maintain the tablet weight constant. Powder were mixed and lubricated with 1% (W/W) magnesium stearate and then directly compressed on a sixteen station compression machine tablet machine at a tablet weight of 350 mg, with a flat, non-beveled punch of 12-mm diameter.

In the wet granulation technique, 160 mg of Valsartan sodium and add each of the polymers (HPMC, Vinyl pyrolidone vinyl acetate and Ethyl cellulose) in the ratio as 1:0.25, 1:0.50 and 1:0.75 were granulated with an Polivinyl pyrolidone (Binder). Granulates were passed through an 18 mesh screen and dried at 40°C for 2 hours. The dried granulate was mixed with other formulation components Micro crystalline cellulose (Diluent), 1.6 mg Magnesium stearate and Talc. Then compressed into flat tablets of 12 mm diameter.

Table No: 6 Formulation Design of Sustained Release Tablets of Valsartan Sodium

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
VS	160	160	160	160	160	160	160	160	160
HPMC	40	80	120	-	-	-	-	-	-
KOLLIDON	-	-	-	40	80	120	-	-	-
EC	-	-	-	-	-	-	40	80	120
PVP	8	8	8	8	8	8	8	8	8
MCC	137.2	97.2	57.2	137.2	97.2	57.2	137.2	97.2	57.2
MS	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
TALC	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2	3.2
Total	350	350	350	350	350	350	350	350	350

VS : Valsartan Sodium

HPMC : Hydroxy Propyl Methyl Cellulose

EC : Ethyl Cellulose

PVP : Poly Vinyl Pyrrolidone

MCC : Micro Crystlline Cellulose

MS : Magnesium Stearate

All the quantities are taken in mg.

7. EVALUATION STUDIES

7.1. IN PROCESS EVALUATION OF GRANULES[36]

1. Angle of repose
2. Determination of bulk density and tapped density
3. Carr's index
4. Hausner's ratio

7.2. EVALUATION OF TABLETS[37]

1. Thickness
2. Hardness
3. Friability test
4. Weight variation test
5. Disintegration
6. *In-vitro* dissolution

7.1. In Process Evaluation of Granules

a) Angle of Repose

The angle of repose of granules was determined by the funnel-method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone measured and angle of repose was calculated using the following equation .

$$\mathbf{Tan\ \theta = h/r}$$

Where,

h and r are the height and radius of the powder cone, θ is the angle of repose

Table No: 7 Relations between Angle of Repose and Flow of the Particles

Angle of repose (degrees)	Type of flow
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very poor

Table No: 8 Angle of repose of Granules

S. No.	Formulation	Angle of repose
1	F1	25.49
2	F2	26.24
3	F3	29.05
4	F4	26.97
5	F5	29.25
6	F6	32.27
7	F7	27.86
8	F8	28.26
9	F9	31.23

b) Determination of Bulk Density and Tapped Density

An accurately weighed quantity of the granules/ powder (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tabs and after that the volume (V_f) was measured and continued operation till the two readings were equal.

The bulk density and the tapped density were calculated using the following formula.

Bulk density = $\mathbf{W/V_0}$

Tapped density = $\mathbf{W/V_f}$

where, W= Weight of the powder

V_0 = Initial volume

V_f = Final volume

C) Compressibility Index (Carr's Index)

Carr's index (CI) is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is.

CI = (TD-BD) x 100/TD

where, TD is the tapped density and

BD is the bulk density

Table No: 9 Carr's Index Values

S.No.	Carr's Index	Properties
1	5-12	Free flowing
2	13-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

d) Hausner's Ratio

It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to interparticle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index .

Table No: 10 In Process Evaluation of Granules

S. No.	Formulation	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Hausner's ratio
1	F1	0.214	0.451	14.74	1.17
2	F2	0.308	0.464	15.38	1.18
3	F3	0.276	0.522	14.28	1.16
4	F4	0.341	0.488	12.11	1.13
5	F5	0.324	0.476	13.82	1.16
6	F6	0.320	0.597	15.39	1.24
7	F7	0.264	0.532	13.24	1.11
8	F8	0.282	0.498	16.75	1.21
9	F9	0.362	0.567	14.32	1.19

7.2. Evaluation of Prepared Tablets

1. Thickness

Five tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper. Average thickness and standard deviation values were calculated

2. Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch five tablets were measured for the hardness and average of six values was noted along with standard deviations.

3. Friability Test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friablator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss.

Note: No tablet should stick to the walls of the apparatus. If so, brush the walls with talcum powder. There should be no capping also.

Percentage friability was calculated as follow

$$\textbf{Percentage Friability} = (W_1 - W_2) \times 100/W_1$$

Where W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.

Friability values below 0.8% are generally acceptable.

4. Weight Variation Test

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

$$\% \text{ weight variation} = (W_A - W_I) \times 100 / W_A$$

As the total tablet weight was 350 mg, according to IP 1996, out of twenty tablets ±7.5 % variation can be allowed for not more than two tablets.

According to USP 2004, ±10% weight variation can be allowed for not more than two tablets out of twenty tablets.

5. Disintegration

Disintegration of a tablet means to break the tablet into smaller particles after swallowing the time required to disintegrate the tablet is called "Disintegration Time". The rate of disintegration depends upon the type of tablet. The tablets which are dissolved by slow solution in the mouth or chewed or are to be dissolved in water before administration, do not need disintegration test. The test was performed for Sustained Release tablets of Valsartan Sodium six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 4 hr and the basket was lift from the fluid, observe whether all of the tablets have disintegrated .

STANDARDS: Out of six tablets five tablets should be disintegrate

Table No: 11 Evaluation of Prepared Tablets

S. No.	Formulation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)
1	F1	6.22	5.50	0.36	349.8±1.48
2	F2	6.37	5.50	0.39	350± 0.54
3	F3	6.14	5.58	0.12	349.6±0.41
4	F4	6.20	5.66	0.41	348.8±1.64
5	F5	6.08	4.25	0.54	348.6±1.14
6	F6	6.33	4.08	0.58	349.2±0.83
7	F7	6.13	4.12	0.34	347.2±0.12
8	F8	6.21	5.42	0.46	348.9±0.23
9	F9	6.25	5.31	0.51	349.3±0.39

6. *Invitro* Drug Release Characteristics

Drug release was assessed by dissolution test using USP type II dissolution apparatus (paddle method) at 100 rpm in 900ml phosphate buffer pH 6.8 from 1 to 12 hours, maintained at 37°C ± 0.5°C.

An aliquot (5ml) was withdrawn at specific time intervals and replaced with the same volume of pre warmed (37°C ± 0.5°C) fresh dissolution medium.

The samples withdrawn were filtered through Whatmann filter paper (No.1) and drug content in each sample was analyzed by UV-visible spectrophotometer at 249 nm.

Table No: 12 *In-vitro* Dissolution Profile for Formulation F1

Time (Hrs)	Cumulative Percentage Drug Release
1	07.47
2	10.70
4	12.30
6	24.07
8	53.61
10	70.42
12	94.92

Graph No: 6 Cumulative Percentage Drug Release Vs Time

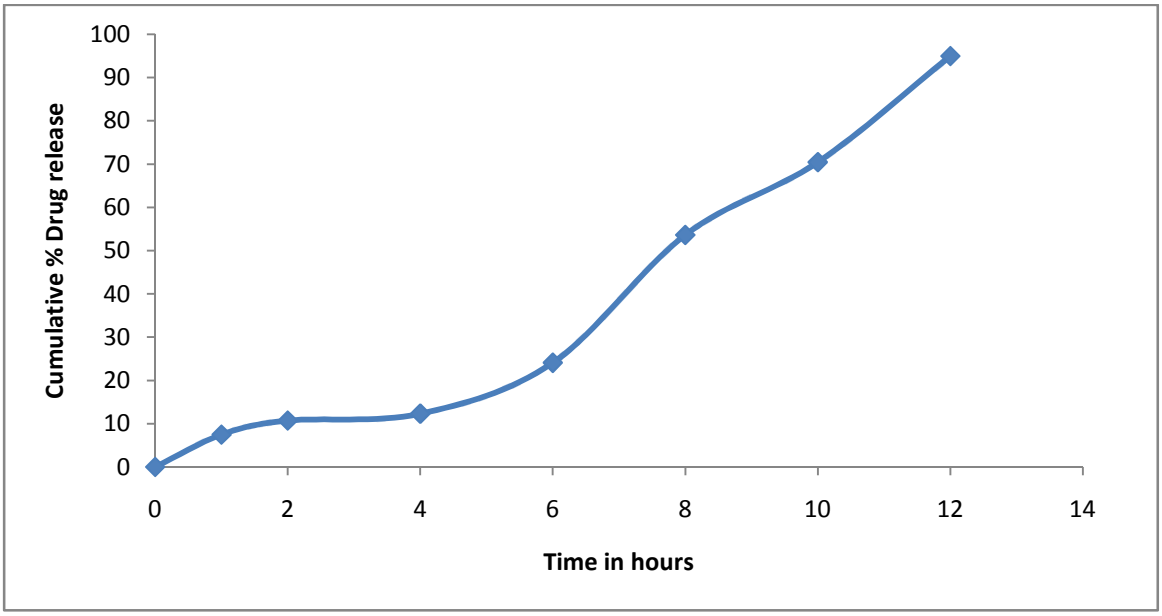


Table No: 13 *In-vitro* Dissolution Profile for Formulation F2

Time (Hrs)	Cumulative Percentage Drug Release
1	9.44
2	18.01
4	26.36
6	31.42
8	51.85
10	74.70
12	92.50

Graph No: 7 Cumulative Percentage Drug Release Vs Time

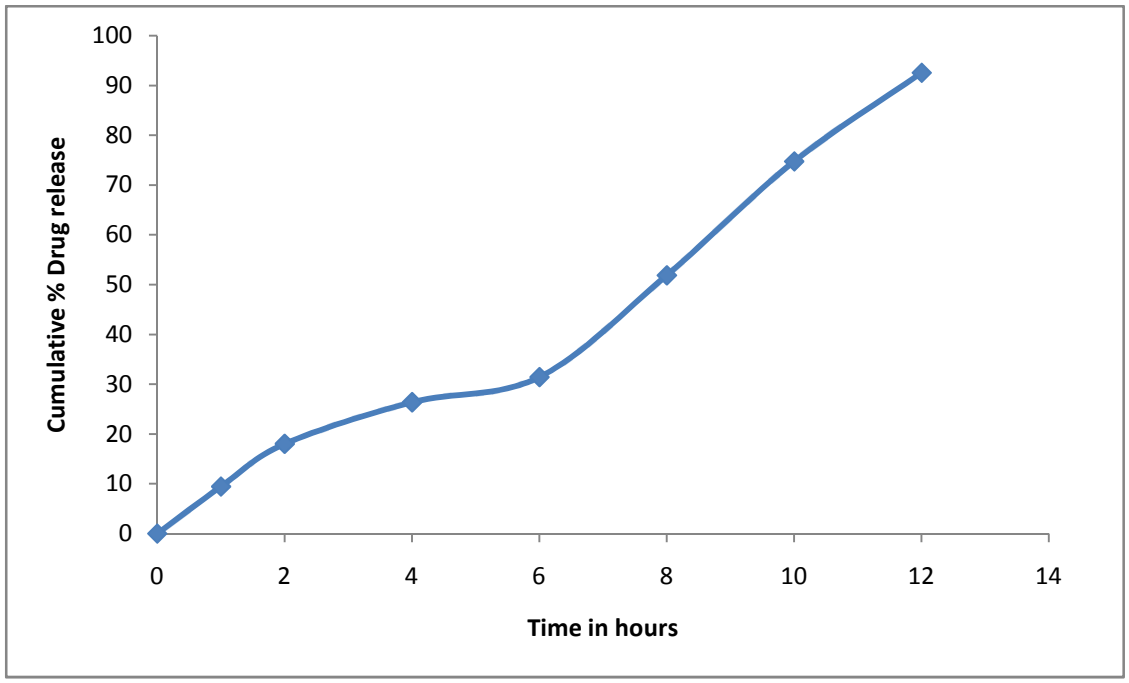


Table No: 14 *In-vitro* Dissolution Profile for Formulation F3

Time (Hrs)	Cumulative Percentage Drug Release
1	5.19
2	14.92
4	24.01
6	32.66
8	42.83
10	70.52
12	91.08

Graph No: 8 Cumulative Percentage Drug Release Vs Time

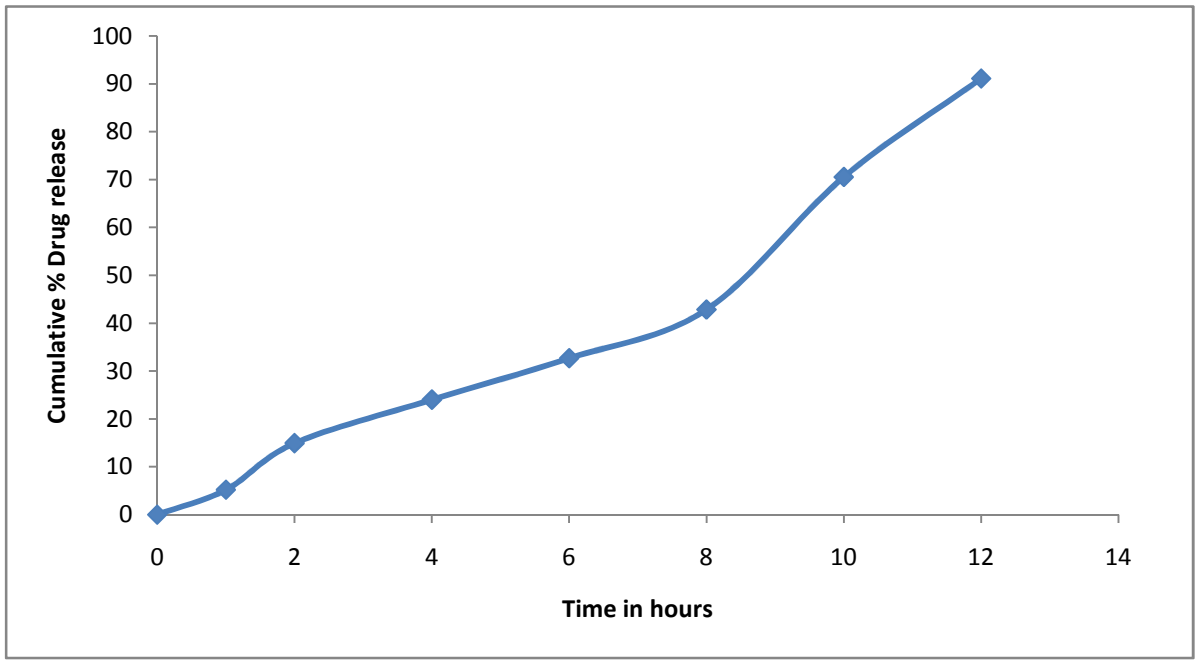


Table No: 15 *In-vitro* Dissolution Profile for Formulation F4

Time (Hrs)	Cumulative Percentage Drug Release
1	8.34
2	15.60
4	28.12
6	43.20
8	62.84
10	86.13
12	98.87

Graph No: 9 Cumulative Percentage Drug Release Vs Time

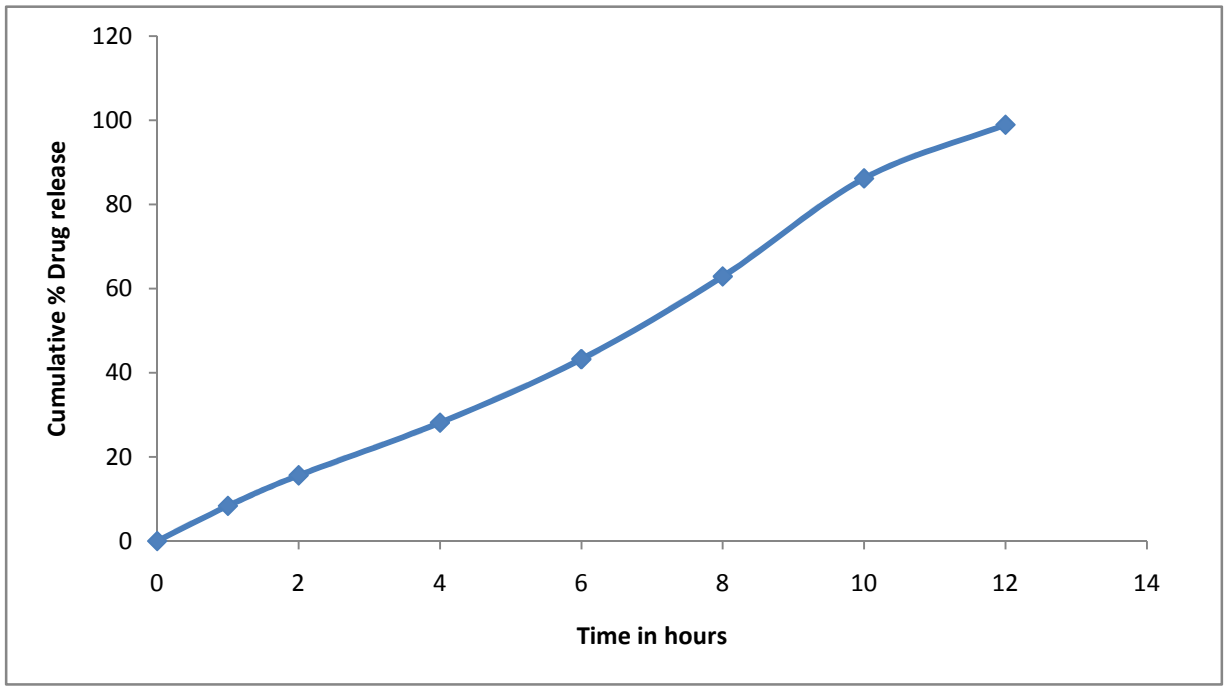


Table No: 16 *In-vitro* Dissolution Profile for Formulation F5

Time (Hrs)	Cumulative Percentage Drug Release
1	6.811
2	16.40
4	21.53
6	30.32
8	43.50
10	59.10
12	94.04

Graph No: 10 Cumulative Percentage Drug Release Vs Time

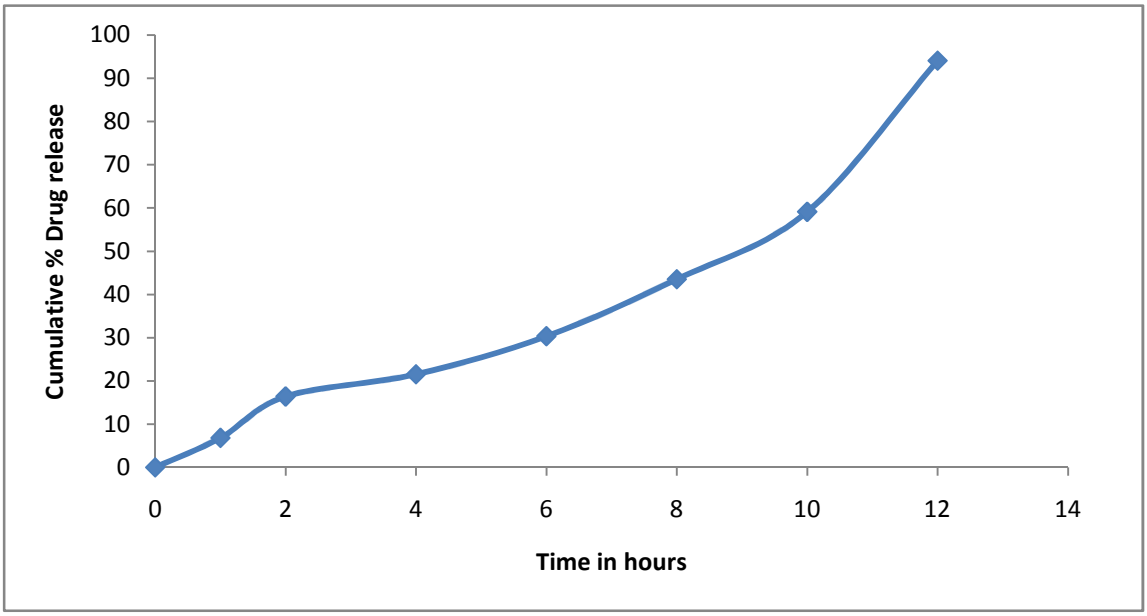


Table No: 17 *In-vitro* Dissolution Profile for Formulation F6

Time (Hrs)	Cumulative Percentage Drug Release
1	6.05
2	15.57
4	26.17
6	35.04
8	65.92
10	80.48
12	96.05

Graph No: 11 Cumulative Percentage Drug Release Vs Time

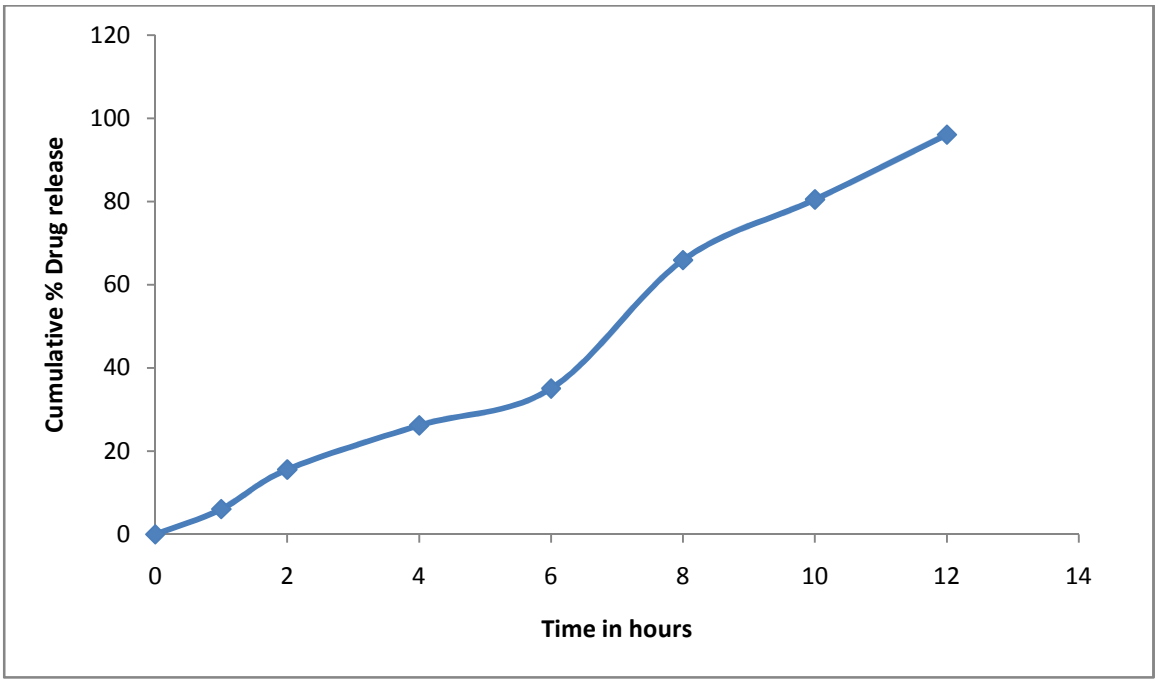


Table No: 18 *In-vitro* Dissolution Profile for Formulation F7

Time (Hrs)	Cumulative Percentage Drug Release
1	10.10
2	16.04
4	21.48
6	41.08
8	64.16
10	84.81
12	96.89

Graph No: 12 Cumulative Percentage Drug Release Vs Time

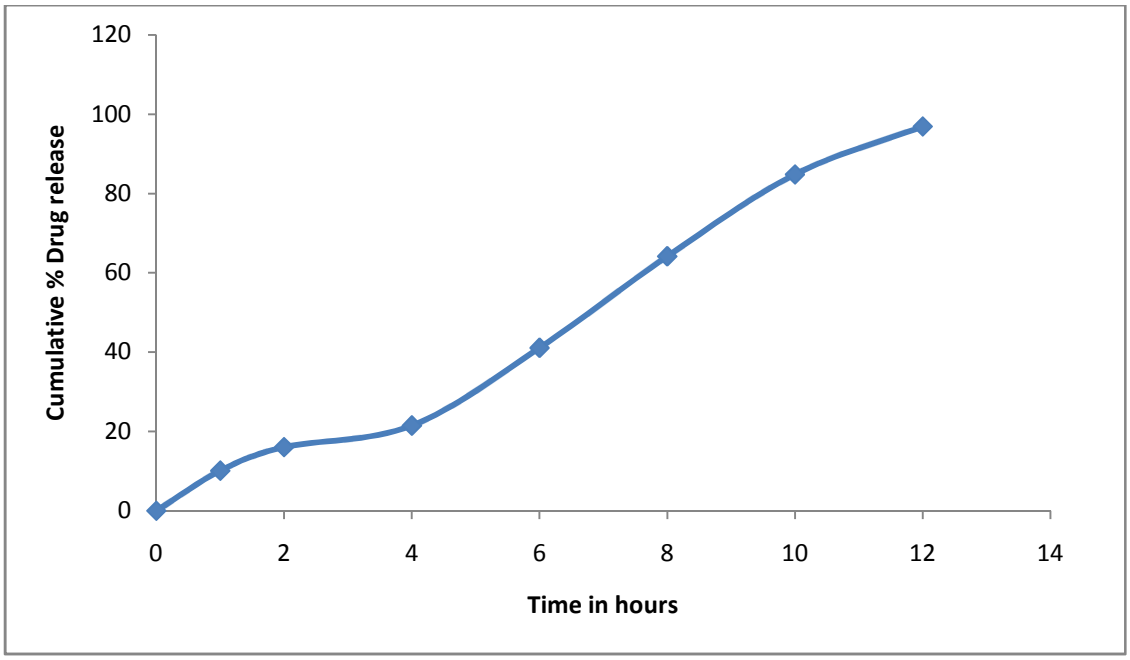


Table No: 19 *In-vitro* Dissolution Profile for Formulation F8

Time (Hrs)	Cumulative Percentage Drug Release
1	7.03
2	14.6
4	21.09
6	27.90
8	47.02
10	79.54
`12	92.06

Graph No: 13 Cumulative Percentage Drug Release Vs Time

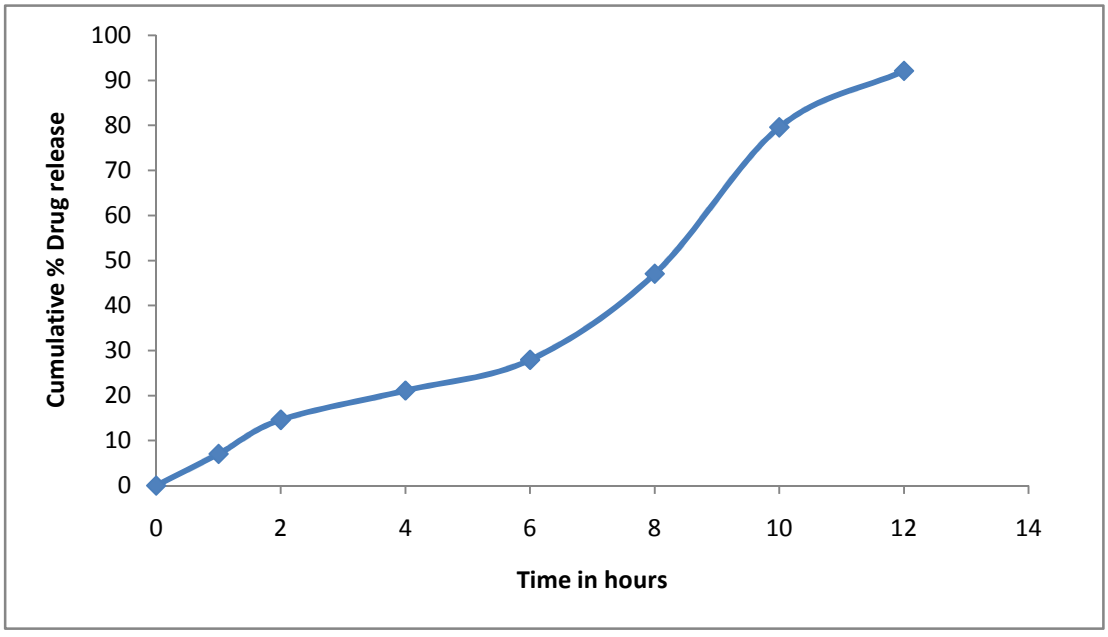


Table No: 20 *In-vitro* Dissolution Profile for Formulation F9

Time (Hrs)	Cumulative Percentage Drug Release
1	7.13
2	15.36
4	26.82
6	38.50
8	46.08
10	77.66
12	94.54

Graph No: 14 Cumulative Percentage Drug Release Vs Time

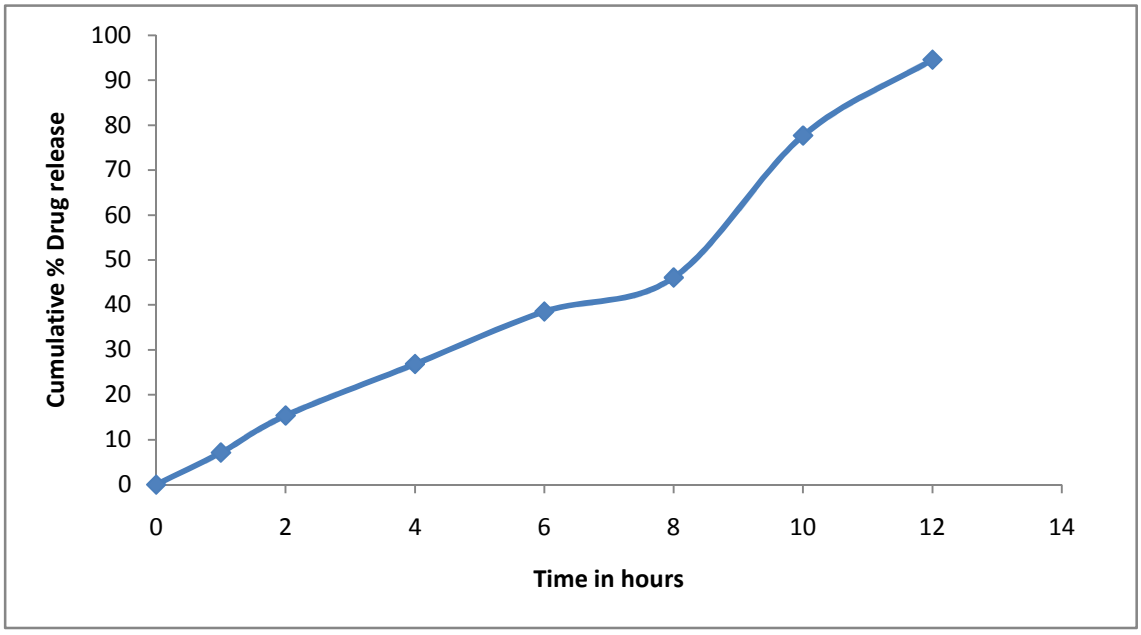
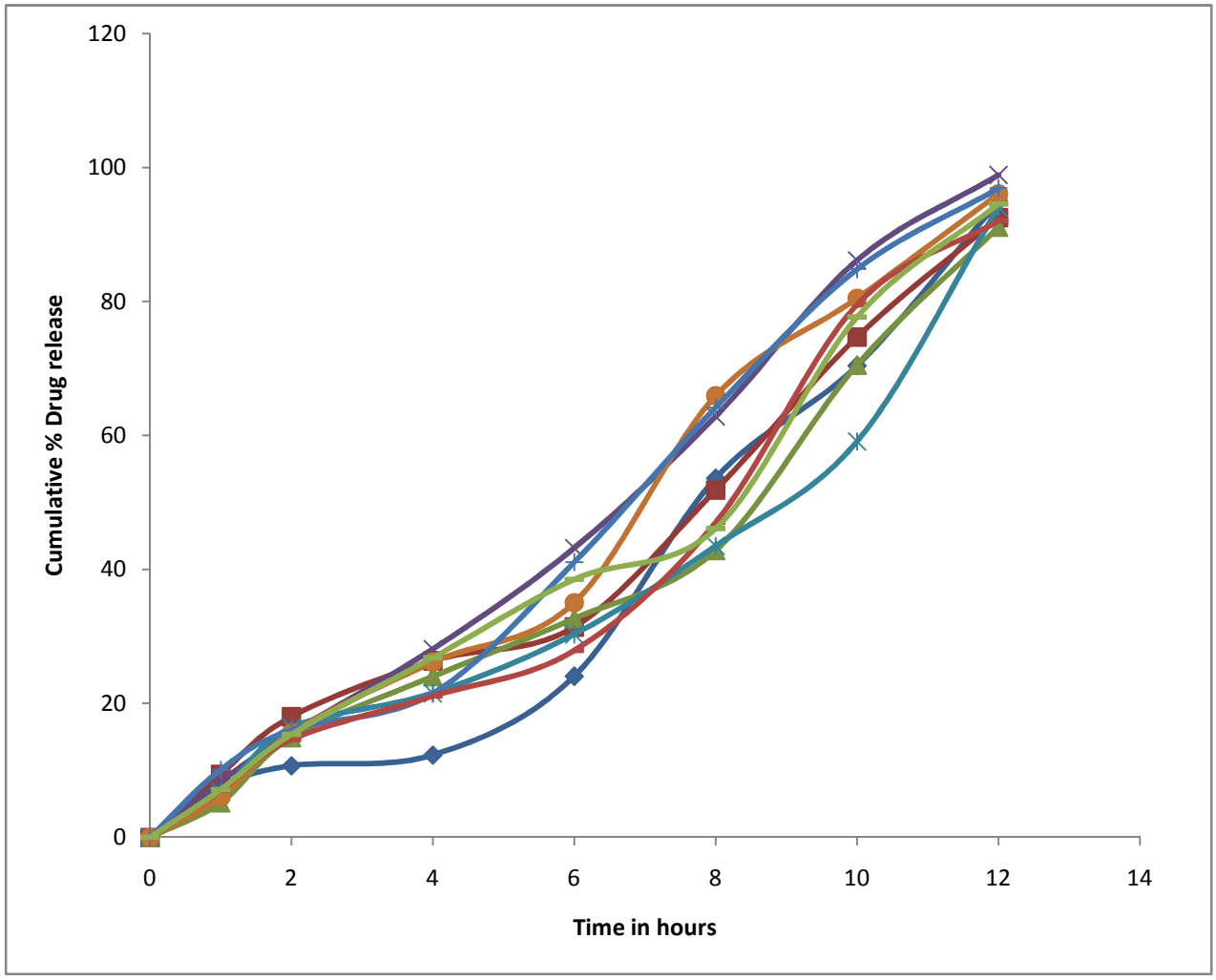


Table No: 21 Cumulative % Drug Release Vs Time

Cumulative Percentage Drug Release									
Time (hrs)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
1	7.47	9.44	5.19	8.34	6.811	6.05	10.10	7.03	7.13
2	10.7	18.01	14.92	15.60	16.40	15.57	16.04	14.6	15.36
4	12.30	26.36	24.01	28.12	21.53	26.17	21.48	21.09	26.82
6	24.07	31.42	32.66	43.20	30.32	35.04	41.08	27.90	38.50
8	53.61	51.85	42.83	62.84	43.50	65.92	64.16	47.02	46.08
10	70.42	74.70	70.52	86.13	59.10	80.48	84.81	79.54	77.66
12	94.92	92.50	91.08	98.87	94.04	96.05	96.89	92.06	94.54

Graph No: 15 Cumulative Percentage Drug Release Vs Time (hrs)



8. STABILITY STUDIES

Stability testing

The purpose of stability testing is to asses the effect of temperature, humidity, moisture, light and other environmental factor on the quality of the drug substance or the final product. These results are used to establish the storage condition, test period and shelf life. The overages to be included in the formulation.

The drug may be detoriated due to physical, chemical, and microbial contaminants which will result in the formation of

1. A toxic product

2 . An inelegant product

3. Reduced activity of preparation

The accelerated stability studies are done as described in the International Conference on Harmonization (ICH) Guidelines.

Procedure

The formulations were stored in an oven at 37 $\pm$ 1^0C and 60 $\pm$ 1^0C for a period of three months. The samples were analyzed for various parameters every month by spectrophotometer at 249 nm.

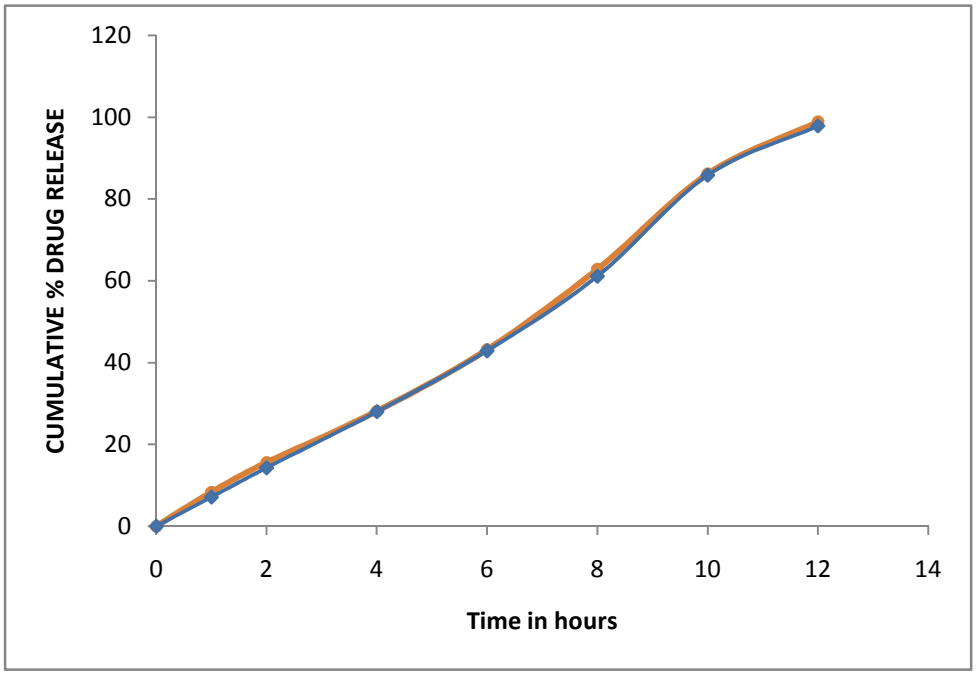
Table No.22 Stability studies of formulation F4

Specification	Initial	30 Days	60 Days	90 Days
Appearance White round tablet	White	No change observed	No change observed	No change observed
Average weight 350 mg ± 2%	350mg	349mg	349mg	348mg
Hardness	5.5 Kg/cm^2	5.5 Kg/cm^2	5.6 Kg/cm^2	5.4 Kg/cm^2
Friability	0.36%	0.36%	0.35%	0.34%

Table No.23 DISSOLUTION STUDY

	Time in (hrs)	Cumulative % drug release	
		Initial	3 Months
		F4	F4
Dissolution Medium 900ml pH 6.8	1	8.34	7.12
	2	15.60	14.28
	4	28.12	27.98
	6	43.20	42.89
	8	62.84	61.11
	10	86.13	85.76
	12	98.87	97.84

Graph No. 16. Cumulative % drug release Vs time during stability studies



9. RESULTS AND DISCUSSION

The procured sample of Valsartan sodium was tested for its identification by using *FT-IR* Spectra study were shown.

The drug and excipient compatibility was done at 25^0C. And Relative Humidity was found to be 60% ± 5%The results does not show any physical change to the mixture after 4 weeks. Chemical compatibility was analyzed by the spectrum study. This fact concluded that the drug and the excipient are compatible with each other was determined using *IR Spectra.*

Before compression of tablets all the polymers were tested with quantity of diluent and lubricant to observe the flow property and the amount was fixed after successive initial trials.

In the present work, total nine formulations were prepared and the detailed composition were shown in **Table No.6**. The prepared pre compression blend was then subjected to various evaluation studies such as Angle of Repose, Carr's Index, Hausner's Ratio, Bulk density, Tapped density, etc., and the results are shown in **Table No.10**

The Prepared tablets were evaluated for various parameters such as Hardness, Friability, Weight Variation, Thickness, In vitro drug release and these results were shown in **Table No.11**

The study was well targeted for sustained release of Valsartan sodium all the criteria of drug was properly studied along with polymer property. Different parameters of tablet like flow property, thickness, hardness, drug content etc., were studied with results in successful trials. The amount of drug release in fixed duration was of more importance and was performed with precision and accuracy and *In Vitro* drug release studies. The utilization of Vinyl pyrrolidone vinyl acetate is to reduce the formulation cost and make it cost effective formulation and increase bioavailability.

10. SUMMARY AND CONCLUSION

Sustained Release tablets were compressed without any problem and do not require any change in ratio of excipients in formulation. Results of the present study demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained release matrix tablets of Valsartan Sodium.

The drug release rate was almost similar with HPMC and plastic Vinyl pyrrolidone vinyl acetate Sustained Release tablets. All the formulations have shown drug release in 12 hrs. The formulation F_4 have been choosen as optimum preparation with higher drug release and enhanced bioavailability. Majority of formulations have released the drug by Non Fickian diffusion.

The formulation with Ethyl Cellulose has shown low drug release and has the problem of dose dumping. The formulation with HPMC has shown similar drug release as that of Vinyl pyrrolidone vinyl acetate but does not follow the theoretical drug release profile. Micro crystalline cellulose used as a diluents does not show any effect on the drug release pattern.

Optimized formulation F4 which includes Vinyl pyrrolidone vinyl acetate has successfully sustained the drug release for 12 hours and the drug release pattern was similar to theoretical release profile.

FT-IR studies combined with stability studies proved the integrity of the developed tablets.

11. BIBLIOGRAPHY

1. DM Brahmankar and SB Jaiswal.,1995, ***Biopharmaceutics and Pharmacokinetics***, Vallabh Prakashan. 337.
2. M. Gwen Jantzen and Joseph R. Robinson., ***Sustained and Controlled-Release Drug-Delivery Systems, Controlled drug delivery. Fundamentals and applications,*** Marcel Dekkar, New York.
3. Leon Shargel, Susanna Wu-Pong, Andrew BC Yu. ***Modified-release drug products. In: Applied Biopharmaceutics & Pharmacokinetics,*** 5th ed. 2004.
4. G. Nicholas Sustained release dosage forms. In: Leon Lachman, Herbert A. Liberman, Joseph LK. ***The Theory and Practice of Industrial Pharmacy.*** 3rd ed. Varghese Publishing House, Bombay. 1987;430-456.
5. Jantzen , Robinson JR. Sustained and controlled drug delivery system. In: Banker G. Rhodes. ***Modern Pharmaceutics***, 3rd ed, Marcel Dekker.1996;921-942.
6. S.P. Vyas and Roop K. Khar., ***Controlled Drug Delivery, Concepts and advances,*** Vallabh prakashan. pp-97-111.
7. Robinson JR, Eriksen SP. Theoretical formulation of sustained-release dosage forms***. J Pharm Sci.*** 1966;55:1254**-**1263**.**
8. Robinson JR, Lee VHL. ***Controlled Drug Delivery: Fundamentals and Applications,*** 2nd ed. New York, Marcel Dekker, Inc.1987.
9. C.P. JAIN AND P.S. NARUKA Formulation And Evaluation Of Fast Dissolving Tablets Of Valsartan ***International Journal of Pharmacy and Pharmaceutical Sciences***, Vol. 1, Issue 1, July-Sep. 2009 219-226.
10. George Vamvakas, Peijin Zhang , Aqeel Fatmi, Shingai Majuru Development of Self Emulsifying Drug Delivery System (SEDDS) for Valsartan and Bioavailability Assessment 2010 ***Banner Pharmacaps, Inc***. CRS 2010-02-GV.
11. Abdel Naser ZAID, Rita CORTESI, Aiman QADDOMI, Saed KHAMMASH Formulation and Bioequivalence of Two Valsartan Tablets After a Single Oral Administration ***Sci Pharm***. 2010; 79: 123–135.

12. Amelia Avachat and Vikram Kotwal. Design and Evaluation of Matrix-Based Controlled Release Tablets of Diclofenac Sodium and Chondriotin Sulphate. ***AAPS PhramSciTech.*** 2007; 8(4): E1-E6.
13. K.Raghuram Reddy A Factorial Study on the Effects of β Cyclodextrin and Poloxamer 407 on the Dissolution Rate of Valsartan from CD Complexes and their Tablets July – September 2011 ***RJPBCS*** Volume 2 Issue 3 438-444.
14. Chinam Niranjan Patra ***An overview of controlled-release systems.*** In: wise DL.ed, Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker. 2000.
15. Bhalla and Handa A.K. Development and Evaluation of controlled release tablets of Carbamazepine. ***Indian Drugs***. 1999; 36(2).
16. S. Indumathy and Kavimani S Anti Inflammatory Activity Of Angiotensin Antagonists ***Pharmacie Globale© (IJCP)***, Vol. 02, Issue 01 Page No 1-2.
17. Parikh Bhavik Anjankumar Design And Evaluation Of Buccal Patches Of Valsartan

    Vol 1: 2 (2010) ***IJPI's Journal of Pharmaceutics and Cosmetology*** 50-55.

18. K. Venkatesh kumar, N. Arun kumar, Prp. Verma, C. Rani Preparation And In Vitro Characterization Of Valsartan Solid Dispersions Using Skimmed Milk Powder As Carrier ***International Journal Of Pharmtech Researc Coden(Usa):*** ijprif issn : 0974-4304 vol.1, no.3, pp 431-437 , July-Sept 2010.
19. Carlos Eduardo de Matos Jensen, Robson Augusto Souza dos Santos, Angelo Márcio Leite Pharmaceutical Composition of Valsartan:β-Cyclodextrin: Physico–Chemical Characterization and Anti-Hypertensive Evaluation. ***IJPI's Journal of Pharmaceutics and Cosmetology*** 87-91Government of India Ministry of Health and Family Welfare. ***The Pharmacopoeia of India.*** Delhi, India: Controller of Publication; 1996.
20. D. Srinivas, Subal Debnath, T.R.S Chowdary, S.Y. Manjunath *Formulation and evaluation of Valsartan film coated tablets* ***J. Chem. Pharm. Res.,*** 2011, 2(5):534-540
21. R. Agnivesh Shrivastava, Bhalchandra Ursekar and Chhanda J. Kapadia Design, Optimization, Preparation and Evaluation of Dispersion Granules of Valsartan and Formulation into Tablets ***Current Drug Delivery,*** 2011, *Vol. 6, No. 1* 28-37.

22. P. Mahajan, S.C.Mahajan and D.K.Mishra Valsartan release from sustained release matrix tablet and effect of cellulose derivatives ***Int. J. of Pharm. & Life Sci. (IJPLS),*** Vol. 2, Issue 1: Jan: 2011, 521-530.
23. M. Soumya , M. Saritha Preparation And Optimisation Of Valsartan Bilayered Sustained Release Matrix Tablets ***International Journal of Pharmaceutical & Biological Archives*** 2011; 2(3):914-920.
24. Jaber Emami, Naser Tavakoli. Formulation of sustained-release lithium carbonate matrix tablets: influence of hydrophilic materials on the release rate and in vitro-in vivo evaluation. ***J Pharm Pharmaceut Sci***. 2004; 7(3):338-344.
25. Anjan K. Mahapatra, P. N. Murthy, Sudarsan Biswal, Dissolution Enhancement and Physicochemical Characterization of Valsartan in Solid Dispersions with β-CD,HP β-CD, and PVP K-30 ***.Dissolution Technologies*** February 2011, 39-45.
26. Mandadi Sunitha and Vikram Kotwal, **Design and Evaluation of Matrix Based Controlled Release Tablets of Diclofenac Sodium and Chondroitin Sulphate,** ***AAPS Pharm Sci Tech***, 8 (4) (2011) E3.
27. Korsmeyer , Gurny R, Doelker E, Buri P. Peppas NA. Machanisms of solute release from porous hydrophilic polymers. ***Int J Pharm***. 1983;15:25-35.
28. KPR Chowdary K Surya Prakasa Rao A Factorial Study on the Effects of β Cyclodextrin and Poloxamer 407 on the Dissolution Rate of Valsartan from CD Complexes and their Tablets July – September 2011 ***RJPBCS*** Volume 2 Issue 3 438-444.
29. Sh Lakade And Mr Bhalekar Formulation And Evaluation Of Sustained Release Matrix Tablet Of Anti-Anginal Drug, Influence Of Combination Of Hydrophobic And Hydrophlic Matrix Former ***research j. Pharm. And tech***. *1(4): OCT.-DEC. 2011, 410-413.*
30. Raghavendra rao , gandhi sagar , patel tarun Formulation And Evaluation Of Sustained Release Matrix Tablets Of Tramadol Hydrochloride ***International Journal of Pharmacy and Pharmaceutical Sciences,*** Vol. 1, Suppl 1, Nov.-Dec. 2011.
31. Lachman L, Lieberman HA, Kanig JL. ***The Theory and Practice of Industrial Pharmacy.*** Philadelphia, PA: Lea and Febiger. 1987;317-31
32. Gulam Irfani**,** Raga Sunil raj, Design And Evaluation Of Transdermal Drug Delivery System Of Valsartan Using Glycerine As Plasticizer ***IJPRD/2011/PUB/ARTI/***VOV-3/ISSUE-2/APRIL/023.

33. V. Pillay , Fassihi R. Electrolyte-induced compositional heterogeneity:a novel approach for rate-controlled oral drug delivery. ***J Pharm Sci.*** 1999; 88(11):1140-1148.
34. British Pharmacopoeia, 2009. Volume-I, pp 937-938.
35. European Pharmacopoeia, 6.0, Volme-2. pp 1974-1975.
36. Indian Pharmacopoeia, Volume-2.
37. L. Lachman , Lieberman HA, Kanig JL. ***The Theory and Practice of Industrial Pharmacy. Philadelphia***, PA: Lea and Febiger. 1987;317-318.
38. CM. Lopes, Lobo JMS, Costa P, Pinto JF. **directly compressed mini matrix tablets containing ibuprofen: preparation and evaluation of sustained release**. ***Drug Dev Ind Pharm.*** 2006;32:95-106.
39. Paul JS, Ryan TR, Ryan DM, Brent MB. Effects of lubricant level, method of mixing, and duration of mixing on a controlled-release matrix tablet containing hydroxypropylmethylcellulose. ***Drug Dev Ind Pharm.*** 1995;21(19):2151-2165.
40. NA. Peppas. Analysis of fickian and non-fickian drug release from polymers. ***Pharm Acta Helv***. 1985;60:110-111.
41. Rang and Dale. ***Text book of Pharmacology.***1265-1273
42. Robinson JR, Eriksen SP. Theoretical formulation of sustained-release dosage forms**.** ***J Pharm Sci.*** 1966;55:1254-1263**.**
43. M. Saleh, Al-Saidan, Krishnaiah YSR, Srinivas Patro S, Satyanarayana V. in vitro and in vivo evaluation of guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. ***AAPS PharmSciTech.*** 2005;6(1):E5.
44. R. Selim, Mohiuddin AQ, Syed SH. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery**.** ***J Pharm Pharmaceut Sci.*** 2003;6(2):282-291.
45. Sinju Engineer, Zezhi JS, Nouman AK. Temperature/Humidity sensitivity of sustained-release formulations containing kollidon® SR. ***Drug Dev Ind Pharm***. 2004;30(10):1089-1094.
46. S. Venkataraman, Davar N, Chester A, Kliene L. ***An overview of controlled-release systems.*** In: wise DL.ed, Handbook of Pharmaceutical Controlled Release Technology, Marcel Dekker. 2000.